4.2.12.2d Analyses of Study 033 Trial Results

Secondary study objectives (cont):

3. Changes in plasma renin activity between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7.

At day one, plasma renin activity fell in all groups after administration of study drug (including placebo). There was no significant differences detected between placebo and any of the active drug groups.

At day seven, plasma renin activity levels fell significantly after administration of study drug in both of the celecoxib groups and in the naproxen group, relative to the placebo group (which rose slightly). There was no significant difference between the changes seen in either of the celecoxib groups and the naproxen group.

Table 4.2.12.2d.5 Effect of celecoxib and naproxen on plasma renin activity in study #033[a].

	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10	P-value
DAY ONE					
Baseline (30 mins Predose)					
Mean±SD	1.8±0.4	2.3±1.5	1.6±0.8	1.8±0.3	--
Range	(b)(4)				--
Difference from Pre- to Post-Dose					
Mean±SD	-0.38±0.34	-0.41±0.53	-0.48±0.42	-0.41±0.31	0.582[b]
Range	(b)(4)				
DAY SEVEN					
Baseline (30 mins Predose)					
Mean±SD	1.1±0.5	1.0±0.7	0.87±0.5	0.76±0.3	--
Range	(b)(4)				
Difference from Pre- to Post-Dose					
Mean±SD	+0.26±0.47	-.114±0.27	-0.166±0.3	-0.116±0.3	0.013
Range	(b)(4)				

a. Data from NDA volume 1.137, table 14.

b. Using ANCOVA, per the sponsor.

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4.2.12.2d Analyses of Study 033 Trial Results

Secondary study objectives (cont):

4. Changes in plasma aldosterone and atrial natriuretic peptide levels between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7.

At day one, serum aldosterone levels fell in all treatment groups, with no significant differences seen between active drug and placebo.

At day seven, the pre-dose serum aldosterone levels were lower in all groups when compared with the day one pre-dose value. Serum aldosterone levels also fell after study drug administration, again with no significant differences between the active drug groups (celecoxib or naproxen) and placebo. As with other hormonal measurements in the trial, extremely broad standard deviations reflected large between-subject variability.

Table 4.2.12.2d.6 Effect of celecoxib and naproxen on plasma renin activity in study 033[a].

	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10	P-value[b]
DAY ONE					
Baseline (30 mins Predose)					
Mean±SD	124.5±70	82.5±32	82.4±43	103.6±81	
Range	(b)(4)				
Difference from Pre- to Post-Dose					
Mean±SD	-29.5±93	-4.2±33	-3.9±44	-23.3±47	0.986
Range	(b)(4)				
DAY SEVEN					
Baseline (30 mins Predose)					
Mean±SD	78.8±34	60.4±23	59.5±21	57.0±16	
Range	(b)(4)				
Difference from Pre- to Post-Dose					
Mean±SD	-14.9±30	-14.5±16	-8.1±18	-12.5±17	0.915
Range					

a. Data from NDA volume 1.137, table 18.
b. Using ANCOVA, per the sponsor.

Serum atrial natriuretic peptide levels did not change from normal values at any time during the study, and no significant differences were detected between placebo and active drug groups. See NDA vol. 1.137, table 19 for details.

(b)(4) APPEARS THIS WAY ON ORIGINAL

4.2.12.2d Analyses of Study 033 Trial Results

Secondary study objectives (cont):

5. Changes in fractional urinary sodium, potassium, and lithium clearances between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7.

Fractional excretion of sodium (FeNa)

The first table summarizes the changes in the FeNa from pre-dose day one to pre-dose day 7. For all groups, FeNa rose between the pre-dose on day one and the pre-dose on day 7. There was no significant difference between groups with regard to their effect on FeNa, measured from pre-dose day 1 to pre-dose day 7. There was also no significant difference between the effects of celecoxib (either dose) and naproxen on FeNa.

Table 4.2.12.2d.7 Effect of celecoxib and naproxen on fractional urinary sodium excretion (FeNa) in study #033[a].

	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10	P-value
PRE-DOSE DAY ONE **Baseline (30 mins Predose) Mean±SD**	0.0030±0.0017	0.0039±0.0026	0.0044±0.0036	0.0040±0.0024	0.673
PRE-DOSE DAY SEVEN **Baseline (30 mins Predose) Mean±SD**	0.0043±0.0023	0.0065±0.0050	0.0064±0.0044	0.0056±0.0037	0.647
DIFFERENCE FROM PRE-DOSE DAY 7 TO PRE-DOSE DAY 1 Mean±SD	0.0013±0.0024	0.0026±0.0037	0.0020±0.0020	0.0016±0.0023	0.933
P-value[c]	0.118	0.039	0.011	0.056	

a. Data from NDA volume 1.137, table 21.2.
b. Using ANCOVA, per the sponsor.
c. Using paired T-test, per the sponsor.

Fractional excretion of potassium (FeK)

The FeK tended to rise slightly in all active treatment groups from pre-dose day 1 to pre-dose day 7, and all in the placebo group. The administration of naproxen was associated with a non-significantly higher FeK than either of the celecoxib groups over the same period.

Table 4.2.12.2d.8 Effect of celecoxib and naproxen on fractional urinary potassium excretion (FeK) in study #033[a].

	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10	P-value
PRE-DOSE DAY ONE **Baseline (30 mins Predose) Mean±SD**	0.188±0.055	0.249±0.095	0.225±0.083	0.155±0.039	0.035
PRE-DOSE DAY SEVEN **Baseline (30 mins Predose) Mean±SD**	0.170±0.06	0.271±0.11	0.236±0.09	0.198±0.099	0.075
DIFFERENCE FROM PRE-DOSE DAY 7 TO PRE-DOSE DAY 1 Mean±SD	-0.018±0.042	+0.022±0.096	+0.011±0.117	+0.043±0.091	0.447
P-value[c]	0.223	0.456	0.771	0.128	

a. Data from NDA volume 1.137, table 22.2.
b. Using ANCOVA, per the sponsor.
c. Using paired T-test, per the sponsor.

4.2.12.2d Analyses of Study 033 Trial Results

Secondary study objectives (cont)

Fractional excretion of lithium (FeLi)

There was no significant differences in the changes in FeLi from predose day one and predose day seven. The naproxen group did show a significant trend towards a decrease in FeLi over the same time period.

Table 4.2.12.2d.9 Effect of celecoxib and naproxen on fractional urinary lithium excretion (FeLi) in study 033[a].

	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10	P-value
PRE-DOSE DAY ONE **Baseline (30 mins Predose) Mean±SD**	0.17±0.077	0.19±0.054	0.20±0.038	0.19±0.062	0.60
PRE-DOSE DAY SEVEN **Baseline (30 mins Predose) Mean±SD**	0.21±0.079	0.20±0.084	0.19±0.050	0.14±0.036	0.097
DIFFERENCE FROM PRE-DOSE DAY 7 TO PRE-DOSE DAY 1 Mean±SD	0.04±0.08	0.01±0.09	0.0±0.06	-0.05±0.04	0.057
P-value[c]	0.172	0.760	0.922	0.007	

a. Data from NDA volume 1.137, table 23.2.
b. Using ANCOVA, per the sponsor.
c. Using paired T-test, per the sponsor.

6. Safety and pharmacokinetics of celecoxib in sodium- and volume-depleted healthy subjects.

The reader is referred to the pharmacologist's review for the examination of the pharmacokinetics of celecoxib.

4.2.13 Safety Outcomes

The adverse events, serious adverse events, and subject discontinuations are included in sections 8.1 and 8.2.

The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown below. The number of subjects with any SAE and subject discontinuations due to AEs were

Table 4.2.13.1 Clinical adverse experience (AE) summary from study 033[a].

Clinical event shown as # of subjects (% of exposed subjects)	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10
With Any AE	9(90%)	6(55%)	6(60%)	9(90%)
With Serious AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Discontinued due to an AE	1 (9%)	0 (0%)	0 (0%)	0 (0%)
Discontinued due to Lab AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)

a. Data from NDA volume 1.137.

4.2.13.1 Comparisons of Defined Safety Endpoints

Due to the small sample size, no formal comparisons are performed. The adverse events are included in the overall safety analysis in section 8.1.

4.2.13.2 Comments on Specific Safety Parameters

Deaths

There were no deaths in the trial.

Serious Adverse Events

There were no serious adverse events in the trial.

Discontinuations due to Adverse Events

One subject in the placebo group was discontinued before receiving study drug due to coughing, wheezing, and stridor during an infusion of sinistrine and PAH.

4.2.14 Study 033 Efficacy Summary

This study investigated the short-term effects of celecoxib and naproxen on several parameters of renal function and on the excretion of prostaglandins. The population studied were healthy young subjects who underwent a mild volume and sodium-restriction. Overall, the subjects were not truly volume-depleted, as demonstrated by their high baseline FeNa and relatively low serum renins. There was also tremendous variability from patient to patient, making any interpretation the data from this study difficult.

1. Large inter- and intra-patient variability limited the interpretation of study 033 data.
2. No effects of celecoxib and naproxen on GFR or renal blood flow were detected (table 4.2.12.2d.1 and 4.2.12.2d.3).
3. No significant effects of celecoxib and naproxen on PGE2 excretion were detected.
4. Both naproxen and celecoxib inhibited 6-keto-PGF1-alpha excretion. There was a trend towards a greater inhibition in the higher dose and celecoxib (400 BID) when compared with celecoxib 200 mg BID. Naproxen also had a greater effect to inhibit 6-keto-PGF1-alpha excretion than did either dose of celecoxib (table 4.2.12.2d.2).
5. Both naproxen and celecoxib appeared to decrease serum thromboxane levels at the end of day 7. This effect was nominally significant only for naproxen (see table 4.2.12.2d.4).
6. Both naproxen and celecoxib decreased serum renin levels to similar levels at the end of day 7 (table 4.2.12.2d.6).
7. There were no significant effects of either celecoxib or naproxen on the fractional excretion of either sodium or potassium (tables 4.2.12.2d.7 and 4.2.12.2d.8).

4.2.15 Study 033 Safety Summary

1. There were no deaths and one Serious Adverse Event, unrelated to celecoxib administration.
2. There were no incidences of acute renal failure.

4.2.16 Study 033 Reviewer's Conclusions

With regard to efficacy, this trial in healthy subjects demonstrates that both naproxen and celecoxib inhibit the excretion of 6-keto-PGF_1. While the intent of the trial was to examine the effects of celecoxib in volume-contracted patients, this was not achieved. Both celecoxib and naproxen inhibited serum renin activity and thromboxane levels. No significant effects of either naproxen or celecoxib on GFR, renal blood flow, sodium/potassium excretion, or urinary PGE_2 levels were detected, in part due to wide subject variability.

As regards safety, the trial is underpowered to comment on the occurrence of common renal adverse events. No unexpected toxicities were detected.

4.3 Review of Protocol N49-97-06-036 (abbreviated 'study 036' in this review).

4.3.1 Title of Study

Integrated clinical and statistical report to evaluate the effect of SC-58635 200 mg BID and naproxen 500 mg BID on renal function and urinary prostaglandins in patients with stable chronic renal insufficiency.

4.3.2 Sites of Investigation and Investigators

Study was conducted by 11 investigators at 11 study sites in the U.S., of whom 10 enrolled at least one subject.

4.3.3 Background

Initial protocol: Feb. 4, 1997

Protocol amendments:

There were five protocol amendments, March 7, April 25, May 8, July 9, and August 6, 1997.

1. *March 7, 1997*: amendment had the following purposes:
    a. Change the Medical Monitor and Statistician for this study;
    b. Change the GFR entry criteria and medical history;
    c. Modify sample size calculations;
    d. Have all patients as inpatients; and
    e. Amend CRFs to reflect the above changes.

2. *April 25, 1997*: amendment was for minor administrative changes.

3. *May 8, 1997*: amendment expanded the weight range requirements for inclusion into the study, and modified the serum thromboxane assay instructions.

4. *July 9, 1997*: amendment allowed up to two additional days in the Unit to achieve a steady state urinary sodium level (<120 mEq) prior to receiving study medication, and allowed the use of a measured creatinine clearance may be used in lieu of the Cockroft-Gault Estimation of GFR (inclusion criteria #4).

5. *August 6, 1997*: amendment changed the inclusion criteria, to exclude subjects with serum Crt >3 mg/dl.

4.3.4 Study Design

This was a multiple-center, double-blind, randomized, placebo-controlled, multiple-dose, parallel-group study to compare the changes in the glomerular filtration rate (GFR) and urinary prostaglandins (PGE2 and 6-keto-PGF) after administration of celecoxib or naproxen to patients with stable chronic renal insufficiency. Seventy-five (75) patients with stable chronic renal insufficiency received either celecoxib 200 mg BID, naproxen 500 mg BID or placebo for six consecutive days followed by a single morning dose on Day 7. Patients were evaluated in a 14-day Pretreatment Period, a seven-day Treatment Period and a three-day Posttreatment Period.

Changes in plasma renin activity (PRA), sodium, potassium and creatinine clearances, serum thromboxane B2 (TxB) and urinary 11-dehydro TxB were compared between treatment groups. Plasma concentrations of celecoxib and naproxen and urine concentrations of the celecoxib metabolites were measured and descriptively analyzed with the GFRs.

In the first part of the Pretreatment Period (four to 13 days before the first dose of drug administration), patient eligibility was determined by a medical history, physical examination, 12-lead electrocardiogram, clinical laboratory tests (hematology, biochemistry and urinalysis), and an estimated GFR. If female of childbearing potential, a serum pregnancy test was performed.

Eligible patients received a sodium-restricted diet of 80 mEq for the three baseline visits (Day -3 to Day -1). Twenty-four-hour urine collections were obtained starting on Day -2 and Day -1 for measurement of total volume, sodium, potassium, creatinine, PGs and 11-dehydro TxB. In addition, on Day -1 each patient underwent a physical examination (including pregnancy test if applicable. Signs and symptoms present at that time were recorded. Patients then continued a 80 mEq sodium diet throughout the treatment period. Prior to drug administration on Day 1 of the Treatment Period (Day 1 to Day 7), clinical laboratory tests were drawn, including PRA and serum TxB . Several of these 2 laboratory tests were then reassessed throughout the treatment period (see table below). GFR, sodium, potassium and creatinine clearances were also measured and plasma and urine samples for pharmacokinetic analysis of celecoxib and plasma samples for naproxen were collected on Day 1 and Day 7.

4.3.4 Study Design (cont)

A 24-hour urine collection for urinary PGs and 11-dehydro-TxB2 were collected starting on Day 2 and again starting on Day 6. Weight, blood pressure and pulse will be measured each morning, and adverse symptoms and concomitant medications were recorded throughout the Treatment Period.

In the posttreatment period (Days 8-10), patients had a physical examination, and clinical laboratory assessments.

Safety was assessed by physical examinations, clinical laboratory assessments, weight, blood pressure and pulse, and adverse signs and symptoms.

4.3.5 Primary and Secondary Endpoints

There were no specified primary or secondary endpoints in this phase I-II study.

Primary study objectives:

The primary objective of this study was to determine the effect of celecoxib on renal function in patients with stable chronic renal insufficiency by:

1. Comparing the effects of celecoxib on GFR to naproxen treatment; and
2. Comparing the effects of celecoxib on urinary PGE2 and 6-keto-PGF1-alpha. excretion to naproxen treatment.

Secondary study objectives:

The secondary objectives of this study were to evaluate the effects of celecoxib compared to naproxen treatment on:

1. PRA;
2. Fractional excretion of sodium and potassium;
3. Creatinine clearance;
4. Serum TxB2 (ng/mL); and
5. Urinary 11-dehydro TxB2 excretion.
6. The final secondary objectives of this study were to evaluate the safety and pharmacokinetics (PK) of celecoxib in subjects with stable chronic renal insufficiency.

4.3.6 Number of subjects/ randomization

A total of 75 subjects were enrolled at 10 sites in the study: 25 in the placebo group; 23 in the celecoxib 200 mg BID group; and 27 in the naproxen 500 mg BID group.

4.3.7 Inclusion/ Exclusion Criteria

Inclusion Criteria

1. Been of legal age of consent;
2. If female of childbearing potential, agreed to participate in this study by providing written informed consent, been using adequate contraception since her last menses and used adequate contraception during the study, not been lactating, and had a negative serum pregnancy test within 24 hours prior to receiving the first dose of study medication;
3. Had renal disease [defined as elevated serum creatinine and decreased GFR (see below)];
4. Had a GFR between (b)(4) [redacted] $73m^2$ based on the Cockroft-Gault Estimation or a measured creatinine clearance;
5. Had a stable serum creatinine ≤3.0 mg/dL during the Treatment Period (stable was defined as no change in serum creatinine of ≥1 mg/dL in the past six months);
6. Had discontinued all NSAIDs at least 10 days before the Pretreatment Period with the exception of ≤325 mg aspirin/day;
7. Weighed ≥50 kg and was within (b)(4) [redacted] of ideal body weight (as provided by the Metropolitan Life Insurance Table which is in Appendix 6 of the original protocol); and
8. Had provided documented written informed consent prior to admission to this study.

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Exclusion Criteria

1. Any clinically active systemic diseases which would, in the judgment of the Investigator and in consultation with the Searle Medical Monitor, compromise patient safety or the scientific integrity of the study [other than diabetes and its complications, RA or OA, hypertensive complications and complications secondary to renal disease itself];

2. AST (SGOT) or ALT (SGPT) ≥1.5 x the upper limit of normal at baseline, or any other laboratory abnormalities, other than those related to chronic renal insufficiency, or diabetes, thought to be clinically significant in the opinion of the Investigator;

3. Been diagnosed as having or having been treated for esophageal, gastric, pyloric channel or duodenal ulceration within 30 days prior to receiving the first dose of study medication;

4. Presence of more than moderate anemia (hemoglobin <10 g/dL, hematocrit <30%);

5. Urinary incontinence;

6. A history of renal transplant;

7. If male, an inability to abstain from any sexual activity from 96 hours prior to admission to the unit and continuing throughout the entire length of the study;

8. A known hypersensitivity to NSAIDs, COX inhibitors, sulfonamides, intolerance to lactose or hereditary fructose intolerance;

9. A history of substance abuse, drug addiction or alcoholism within the last three years;

10. Used a tobacco product or consumed alcohol within 48 hours prior to the Pretreatment Period or was unable to abstain from tobacco and alcohol products throughout the entire length of the study;

11. Received any investigational medication within 30 days prior to the Treatment Period or was expected to receive any investigational medication during the study other than celecoxib; and

12. Been previously admitted to this study.

4.3.8 Dosage/ Administration

Patients were randomized to receive either celecoxib 200 mg BID, naproxen 500 mg BID or placebo for six consecutive days followed by a single morning dose on Day 7.

4.3.9 Duration/ Adjustment of Therapy

Patients withdrawn prior to beginning study medication (i.e., Day 1) were to have been replaced. Data collected for any such withdrawn patient was not included in the analyses. If patients withdrew for any reason after beginning study drug, he or she was also replaced, and their safety data were included in the analyses. Patients could have been withdrawn from this study for any of the following reasons:

1. The patient's serum creatinine increased by 50% over Pretreatment assessments;
2. The patient missed more than one dose of study drug;
3. The patient developed symptoms that required medical intervention;
4. The patient had two 24 hour urine samples during the Treatment Period that contained >120 mEq sodium each;
5. The patient developed an intercurrent illness that required non-study drug;
6. The patient withdrew his/her consent;
7. The Investigator determined it to be in the patient's best interest; or
8. Searle discontinued the study.

Concomitant Medications

Use of any medication other than the drug provided for this study was to have been avoided, whenever possible, during the Treatment Period. Use of antineoplastic drugs and chronic analgesics were prohibited. Acetaminophen use was specifically discouraged. In the event that medications other than study drug was used, the drug name, dosage, regimen, reason for therapy and therapy dates were.

4.3.10 Safety and Efficacy Endpoints Measured

Table 4.3.10.1 Timetable for clinical observations and lab measurements in the study 036[a].

	PreTreatment Period				Treatment Period							Post-Treatment Period		
	-13 to -4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10
Informed Consent	X													
History	X													
ECG	X													
Physical Exam	X			X										
Clinical/ Urine labs[b]	X				X		X[c]		c			X		
Serum TxB2, renin activity					X						X			
24 hr Urine Prostaglandins & 11-dehydro TxB2			X	X		X				X				
24 hr Urine Na, K, Crt					X						X			
GFR	X[d]				X						X			
Na, K Clearance					X						X			
Study Drug					X	X	X	X	X	X	X			
Plasma/ Urine PK					X						X	X	X	X
Collection of Signs/Sxs				X										

a. Data from NDA volume 1.139, table 1.

b. Lab work included: (1) A complete blood count (hemoglobin, hematocrit, white blood count and differential, platelet count); (2) Serum chemistries (blood urea nitrogen, creatinine, total bilirubin, SGOT (AST), SGPT (ALT), glucose, LDH, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, total protein, albumin, calcium, phosphorus, creatine kinase); and (3) Urinalysis (specific gravity, pH, RBC/hpf, protein, glucose, ketones, bilirubin).

c. BUN, Na, K, Crt only.

d. Cockroft-Gault derived or using measured urine creatinine clearance.

4.3.11 Statistical Considerations

Demographics and Baseline Characteristics

All randomized patients were included in these analyses. Homogeneity across the three treatment groups in terms of gender and race were analyzed using Fisher's Exact Test. The Kruskal-Wallis Test was used to determine homogeneity across the treatment groups with respect to age, height, weight, and vital signs (blood pressure and pulse).

Patient Population Analyzed

Primary and secondary measures were analyzed using an Intent-to-Treat (ITT) Cohort, defined as all randomized patients who received at least one dose of study drug and were not withdrawn from the study. Additionally, the normalized GFR and secondary urinary fractional excretion variables (sodium and potassium) and creatinine clearances were also analyzed at 60 minute intervals using a Modified ITT Cohort, which excluded patients whose GFR could not be calculated due to missing urine or plasma inulin samples or exceeded 175 mL/min/1.73m^2 .

Evaluation of Renal Function and Pharmacokinetic Measures

Descriptive statistics were computed for all primary and secondary variables. These statistics were presented by treatment group and time. Baseline biological variables were compared across treatment groups using the Kruskal-Wallis Test. All inferential analyses were two sided tests with alpha = 0.05. Statistical inferential comparisons were made between celecoxib200 mg, naproxen 500 mg and placebo on the three primary variables: GFR, urinary PGE2 excretion, and urinary 6-keto-PGF1 alpha excretion. GFR was analyzed as the change from Day 1 predose to Day 7 postdose using 30- and 60 minute intervals. For the 30 minute intervals, 3 predose measurements and 6 postdose measurements were evaluated for both days. The mean of the three predose measurements served as the Baseline, and changes from Baseline were calculated for the six postdose time points. For the 60 minute intervals, one predose measurement and three postdose measurements were evaluated for both days. The predose measurement was the Baseline (0-60 minutes predose), and changes from Baseline were calculated for the three postdose timepoints. The major GFR analysis was a repeated ANOVA for Days 1 and 7.

4.3.11 Statistical Considerations (cont)

Three analyses were performed: the change for Day 1 postdose minus predose; the change for Day 7 postdose minus predose; and the change for Day 7 postdose minus Day 1 predose. The analysis model included treatment as the independent variable and the Baseline GFR as covariate. The protocol specified model with treatment, investigative site, and treatment by site interaction as factors was not used due to the small number of patients enrolled at the majority of investigative sites. Supportive analyses were performed using analysis of covariance (ANCOVA) at each of the postdose time points on Days 1 and 7. Paired treatment comparisons were performed using linear contrasts, and p-values were reported.

Urinary PGE2 and 6-keto-PGF1 alpha excretion were analyzed as the change from Baseline (Day -1) to Days 2 and 6. A repeated measures ANOVA (across Days 2 and 6) was performed using the change from Baseline. ANCOVA was computed separately for the change from Baseline to Days 2 and 6. The independent variables in the analysis models were the same as those described for GFR. Paired treatment comparisons were performed using linear contrasts.

Serum TxB2 and PRA were measured on Days 1 and 7 at 30 minutes predose and 4 hours postdose. ANCOVA was used for the change from Baseline (30 minutes predose); that is, postdose minus predose with the predose values as covariates. ANCOVA was employed separately for the two days. The independent variables in the analysis were the same as those for the GFR. The overall treatment comparison p-value was reported.

Fractional excretion of sodium and potassium, and creatinine clearances were analyzed separately as the change from Day 1 predose to Day 7 postdose. There were three predose measurements and six postdose measurements for both days for the 30 minute interval analysis, and there was one predose measurement and three postdose measurements for both days for the 60 minute interval analysis. The statistical methods were identical to those for GFR.

Urinary excretion of 11-dehydro TxB2 was measured on Days 2 and 6, and the statistical methods were identical to those for PGE2 and 6-keto-PGF1-alpha.

A discussion of the tools used for the pharmacokinetic analysis is deferred to the pharmacology reviewers.

Multiplicity

No adjustment for multiplicity was proposed.

Interim Analyses

There were no interim analyses.

Safety Analysis

Every randomized patient who received at least one dose of study drug was included in the safety analysis. All adverse events were coded and summarized by treatment group. The incidence of treatment-emergent adverse events was tabulated by treatment group and body system, and by frequency of treatment group. Using a paired t-test, clinical laboratory data were tested for significant changes within treatment groups from Baseline to Posttreatment (Day 8). Significant changes were tabulated by treatment group. Clinical laboratory data were summarized and treatments compared using the Kruskal-Wallis . Values outside the normal range were identified, and scatter plots were used to graphically depict results. Shift tables (below, within, and above the normal range) and the Stuart-Maxwell Test or McNemar's Test (depending on the number of non-zero cells) were used to determine significant distributional changes over the course of the study. Shifts in laboratory values were compared across treatments in terms of the number of patients showing an increase, decrease, and no change, with respect to the normal range, using a chi-square test. The following laboratory test values were considered clinically relevant and were summarized for each treatment:

AST (SGOT) and ALT (SGPT): ≥ 3 x upper limits of normal value (ULN)
Alkaline Phosphatase: ≥ 1.25 x ULN
Total Bilirubin: ≥ 1.5 x ULN
Creatinine: ≥1.3 x ULN
BUN: ≥2.0 x ULN
Hematocrit: a decrease ≥ 5 percent points (relative to a patient's Baseline value)
Hemoglobin: a decrease ≥ 2 g/dL (relative to a patient's Baseline value)
WBC: <3000/μL
Platelets: <100,000/μL

4.3.12 Efficacy Outcomes for protocol 036

Primary Measures of Evaluation

The primary evaluation measures were:

1. GFR;
2. Urinary PGE2 excretion; and
3. Urinary 6-keto-PGF1-alpha excretion.

Secondary Measures of Evaluation

The secondary evaluation measures were:

1. PRA;
2. Serum TxB2 concentration;
3. Fractional sodium excretion;
4. Fractional potassium excretion;
5. Creatinine clearance;
6. Urinary 11-dehydro TxB2 excretion;
7. PK analysis; and
8. Safety measures.

4.3.12.1 Subject Demographics & Baseline Characteristics

The demographic and clinical background data for the 75 subjects enrolled in study 036 are summarized below.

Table 4.3.12.1.1 Demographics of study 036[a].

Demographic	Placebo N=25	Celecoxib 200 BIDs N=23	Naproxen 500 BID N=27
Gender			
Male	9	12	15
Female	16	11	12
Race (n (%))			
Caucasian	12 (48%)	9 (39%)	18 (76%)
Black	12 (48%)	14 (61%)	8 (30%)
Hispanic	0 (0%)	0 (0%)	0 (0%)
Other	1 (4%)	0 (0%)	1 (4%)
Age (yrs) (Mean±sd)	66.8±11	63.2±11	65.1±11

a. Data from NDA volume 1.139. Table 4.
b. P value <0.001 comparing two GFRs for celecoxib 200 mg BID group.

In other data, the celecoxib group had significantly higher mean systolic BP (147.1±17 mm Hg) when compared with the placebo group (140.6±17 mm Hg).There was no significant differences in the mean weight, height, pulse rate, or diastolic BP. There was also no significant differences between the three groups with regard to other medical history, including renal disease, hypertension, and diabetes. Finally, baseline renal function, as assessed by 24 hour urine collections for Na, Crt, K, and volume, were not significantly different in the three study groups. As discussed in the previous trials, the subject-to-subject variability was quite large.

4.3.12.2 Disposition of Subjects

The table below shows the disposition of subjects in study 036.

Table 4.3.12.2.1 Summary of subjects entered into study 036[a].

	Placebo	Celecoxib 200 BID	Naproxen 500 BID
Entered	25	23	27
Completed	23 (92%)	22 (96%)	26 (96%)
Discontinued: Total	2 (8%)	1 (4%)	1 (4%)
Protocol Non-compliance	0 (0%)	1 (4%)	0 (0%)
AEs	2 (8%)	0 (0%)	1 (4%)
Other	0 (0%)	0 (0%)	0 (0%)

a. Data from NDA volume 1.139. table 3.

4.3.12.2a Subject Selection

No information is available about subject selection in study 036.

4.3.12.2b Protocol Violations & Deviations

Per the sponsor, several of the subjects enrolled in the trial were later found not to have 'sufficient' renal insufficiency, as specified in the original protocol. A decision was made to allow such subjects in the trial, including subjects whose serum crt was ≤3.0 mg/dl. Overall 26 subjects violated one or more entry criteria (of the 75 total subjects!). The 26 subjects were in the following groups: 9 placebo patients; 7 SC-58635 200 mg BID patients; and 10 naproxen 500 mg subjects.

These violations fell into the following categories, and were felt not to be of sufficient severity to warrant removal from the study.

1) Two patients (one placebo patient and one SC-58635 200 mg BID patient) did not have renal disease, as originally defined as an elevated serum creatinine and specified GFR (Inclusion Criterion

2). Nineteen patients (six placebo patients, five SC-58635 200 mg BID patients, and eight naproxen 500 mg BID patients) did not have a GFR between (b)(4) [redacted] 2 based on the Cockroft-Gault estimation, or a measured creatinine clearance (Inclusion Criterion 4).

3) Six patients (two placebo patients, two celecoxib 200 mg BID patients, and two naproxen 500 mg BID patients) did not have a serum creatinine (b)(4) [redacted] males or females during the Pretreatment Period; Inclusion Criterion

4) Six patients (two placebo patients, two celecoxib 200 mg BID patients, and two naproxen 500 mg BID patients) did not have a body weight ≥50 kg and (b)(4) [redacted] of ideal body weight (Inclusion Criterion 7).

5) Two placebo patients and one celecoxib patient had moderate anemia as defined by a hemoglobin <10 g/dL and hematocrit <30% during screening or prior to entering the study.

6) One celecoxib patient had an SGPT >1.5 ULN upon entry into the study. One celecoxib 200 mg BID patient (0007-0112) had two 24 hour urinary sodium excretion values that each were >120 mEq.

4.3.12.2c Concomitant Therapies used after Trial Initiation

No concomitant medications were to be used during the trial, and such use constituted a protocol violation.

4.3.12.2d Analyses of Study 036 Trial Results

Primary study objectives

1. Compare the changes in GFR from pre- to post-dose measurements of Day 1 and Day 7 between celecoxib and naproxen treatment groups.

The effect of short-term administration of celecoxib on GFR was first analyzed by comparing the average GFRs taken before the first dose Days 1 and 7. The sponsor noted wide variability at the 30 minute time point, which was averaged with the pre-dose value to obtain the baseline GFR. To correct this, the results of 60 minute GFRs were analyzed with the pre-dose values in order to obtain a more satisfactory 'mean baseline GFR.' There were no significant differences between the study groups detected, and no significant decline in mean GFR detected in any dose group. When examined hour by hour (data not shown), no consistent effect of any drug or dose –group on GFR was detected. There was also no evidence of a temporal association between plasma levels of celecoxib and naproxen and changes in GFR.

Table 4.3.12.2d.1 Effect of celecoxib and naproxen on GFR in study 036[a].

	Placebo N=25	Celecoxib 200 BID N=23	Naproxen 500 BID N=27
Day One Pre-dose			
Mean±SD	31.8±8.6	31.5±16	36.9±12
Range	18 to 51	5 to 78	16 to 61
Day Seven Pre-Dose			
Mean±SD	34.4±16	35.4±14	37.0±16
Range	15 to 68	11 to 61	7 to 77

a. Data from NDA volume 1.139, table 10.

4.3.12.2d Analyses of Study 036 Trial Results

Primary study objectives (cont)

2. Compare the changes in urinary PGs (PGE_2 and 6-keto-PGF1-alpha, a metabolite of prostacyclin, PGI_2) from predose through pre-dose on Day 7, between the celecoxib and naproxen treatment groups.

Urinary PGE2

For urinary PGE2, there was a statistically significant difference between study drug groups between the Pre-dose values for Days 1 and 7. As shown in the table below, there was a significantly greater decrease in PGE2 excretion in the naproxen group from day one to day 6 than in the placebo group (shown as shaded). There was also a trend towards a decrease in the celecoxib group (within large standard deviations). No significant difference between the naproxen and celecoxib groups was detected.

Table 4.3.12.2d.2 Effect of celecoxib and naproxen on PGE2 excretion in study 036[a].

	Placebo N=25	Celecoxib 200 BID N=23	Naproxen 500 BID N=27
Day One Pre-dose			
Mean	398.8±674	445.6±874	623.3±623
Range	(b)(4)		
Day Six Pre-Dose			
Mean±SD	381.5±445	227.2±352	132.5±131
Range	(b)(4)		
Change from Baseline			
Mean±SD	-36.1±843	-231.8±568	-509.6±1398[b]
Range	(b)(4)		

a. Data from NDA volume 1.139, table 11.

b. P-value <0.05 using Repeated Measures ANOVA vs. placebo.

Urinary 6-keto-PGF1-alpha

Analysis of the 6-keto-PGF1-alpha excretion was again hindered by extremely wide subject to subject variability. This can be seen below in the wide standard deviations and ranges for the 6-keto-PGF1-alpha excretion (at Day –1 and 6). The table below shows the changes from baseline for the study groups at day 6. Despite the broad standard deviations and ranges of individual excretion rates, there was a significantly lower 6-keto-PGF1-alpha in both the celecoxib and naproxen groups, compared with placebo. There was no significant difference between the effects of celecoxib and naproxen.

Table 4.3.12.2d.3 Effect of celecoxib/ naproxen on 6-keto-PGF1-alpha excretion in study 036[a].

	Placebo N=25	Celecoxib 200 BID N=23	Naproxen 500 BID N=27
Day One Pre-dose			
Mean	34.1±28	36.9±40	32.2±21
Range	(b)(4)		
Day Six Pre-Dose			
Mean±SD	37.9±23	14.8±12	11.2±13
Range	(b)(4)		
Change from Baseline			
Mean±SD	1.7±23	-23.2±37[b]	-20.9±20 [b]
Range	(b)(4)		

a. Data from NDA volume 1.139, table 10.

b. P-value <0.05 using Repeated Measures ANOVA vs. placebo.

(b)(4) APPEARS THIS WAY ON ORIGINAL

4.3.12.2d Analyses of Study 036 Trial Results

Secondary study objectives:

1. Compare the changes in urinary 11-dehydro thromboxane A2 (TxA2) from baseline through day 6, between the celecoxib and naproxen treatment groups.

At day 6, the decrease in TxA2 excretion in the naproxen group was significantly greater than in either the placebo or the celecoxib group. The TxA2 excretion in the celecoxib group did not differ significantly from placebo, although there was a numerical decline in TxA2 excretion in the celecoxib group.

Table 4.3.12.2d.4 Effect of celecoxib and naproxen on TxA2 excretion in study 036[a].

	Placebo N=25	Celecoxib 200 BID N=23	Naproxen 500 BID N=27
Day Minus One Pre-dose			
Mean	1402±856	1558±1045	1299±736
Range	[redacted]		
Day Six Pre-Dose			
Mean±SD	1756±950	1572±1002	592±522
Range	[redacted]		
Change from Baseline			
Mean±SD	+305±1200	-38.7±651	-731.6±737
Range	[redacted]		

a. Data from NDA volume 1.139, table 10.

b. P-value <0.05 using Repeated Measures ANOVA vs. placebo and vs. celecoxib.

2 Compare the changes in serum thromboxane levels through day 7, between the celecoxib and naproxen treatment groups.

Naproxen caused an immediate (4 hrs) and sustained (7 days) suppression of serum thromboxane levels that differed significantly from both celecoxib and placebo. Celecoxib had no significant effect on serum TxA2 levels. As before, there was a broad subject to subject variability.

Table 4.3.12.2d.5 Effect of celecoxib and naproxen on TxA2 serum levels in study 036[a].

	Placebo N=25	Celecoxib 200 BID N=23	Naproxen 500 BID N=27
Day Minus One Pre-dose			
Mean	55.1±74	33.7±68	64.6±86
Range	[redacted]		
Day Six Pre-Dose			
Mean±SD	70.7±94	37.3±64	3.5±57
Range	[redacted]		

a. Data from NDA volume 1.139, table 1[redacted]

b. P-value <0.05 using Repeated Measures ANOVA vs. placebo and vs. celecoxib.

[redacted]

4.3.12.2d Analyses of Study 036 Trial Results

Secondary study objectives:

3. Changes in plasma renin activity between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7.

At day one, plasma renin activity fell non-significantly by 4 hours after administration of either celecoxib or naproxen. At day seven, plasma renin activity fell non-significantly in the naproxen group (from 2.7 to 1.8), but rose slightly in the celecoxib group. There was no significant difference between the changes seen in either of the celecoxib groups and the naproxen group and placebo.

Table 4.3.12.2d.6 Effect of celecoxib and naproxen on plasma renin activity in study 036[a].

	Placebo N=23	Celecoxib 200 BID N=22	Naproxen 500 BID N=26
DAY ONE			
Baseline (30 mins Predose)			
Mean±SD	2.9±3.9	3.1±2.9	2.7±5.4
Range	(b)(4)		
DAY SEVEN			
Baseline (30 mins Predose)			
Mean±SD	4.6±8.4	2.2±1.7	1.8±3.9
Range	(b)(4)		

a. Data from NDA volume 1.139, table 15.

5. Changes in fractional urinary sodium and potassium clearances between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7.

Fractional excretion of sodium (FeNa)

The first table summarizes the changes in the FeNa from pre-dose day one to pre-dose day 7. For celecoxib and naproxen, FeNa rose significantly between the pre-dose on day one and the pre-dose on day 7. There was no significant difference between celecoxib and naproxen with regard to their effect on FeNa, measured from pre-dose day 1 to pre-dose day 7. The data are again made more difficult to interpret by subject-subject variability.

Table 4.3.12.2d.7 Effect of celecoxib and naproxen on fractional urinary sodium excretion (FeNa) in study 036[a].

	Placebo N=23	Celecoxib 200 BID N=22	Naproxen 500 BID N=26
PRE-DOSE DAY ONE			
Baseline (30 mins Predose)			
Mean±SD	0.0269±0.029	0.0276±000.027	0.0288±0.042
Range	(b)(4)		
PRE-DOSE DAY SEVEN			
Baseline (30 mins Predose)			
Mean±SD	0.023±0.024	0.0273±0.0.025	0.0406±0.0.055
Range	(b)(4)		
DIFFERENCE FROM DAY 7 TO PRE-DOSE DAY 1[b]			
Mean±SD	-0.0077±0.029	+0.0077±0.022	+0.0052±0.02
P-value[c]	0.864	0.033	0.042

a. Data from NDA volume 1.139, tables 16 and 17.
b. Data from Pre-dose Day 1 and Day 7 (0 – 1 hour postdose).
c. Using paired T-test, per the sponsor.

4.3.12.2d Analyses of Study 036 Trial Results

Secondary study objectives (cont):

Fractional excretion of potassium (FeK)

The FeK tended to rise slightly in all active treatment groups from pre-dose day 1 to pre-dose day 7, and all in the placebo group. The administration of naproxen was associated with a non-significantly higher FeK than either of the celecoxib groups over the same period.

Table 4.3.12.2d.8 Effect of study drugs on fractional urinary K^+ excretion (FeK) in study 036[a].

	Placebo N=23	Celecoxib 200 BID N=22	Naproxen 500 BID N=26
PRE-DOSE DAY ONE			
Baseline (30 mins Predose)			
Mean±SD	0.3157±0.17	0.3145±0.12	0.3217±0.21
Range	(b)(4)		
PRE-DOSE DAY SEVEN			
Baseline (30 mins Predose)	0.3729±0.22	0.3016±0.17	0.5814±0.58
Mean±SD	(b)(4)		
Range			
DIFFERENCE FROM DAY 7 TO PRE-DOSE DAY 1[b]			
Mean±SD	-0.0111±0.11	+0.0503±0.15	0.1102±0.34
P-value[c]	0.571	0.372	0.139

a. Data from NDA volume 1.139, tables 16 and 17.
b. Data from Pre-dose Day 1 and Day 7 (0 – 1 hour postdose).
c. Using paired T-test, per the sponsor. Note that difference not calculated from pre-dose values on Days 1 and 7 above.

6. Changes in creatinine clearances between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7.

The table below summarizes the estimated creatinine clearance data from pre-dose Day one and 7, as well as the post-dose day 7, and a comparison of the changes in creatinine clearance from pre-dose day 1 to post-dose day 7. Note the large variability, both between subjects and from time point to time point (e.g.; from 60 minutes pre-dose to 30 minutes pre-dose). Note also that some of the estimated creatinine clearance values are supra-physiologic (e.g.; one subject had an estimated clearance of 323 at 60 minutes pre-dose on day 1). These problems confound interpretation of the data from the study.

Overall, there were no significant differences between treatment groups with regard to changes in creatinine clearance from pre-dose day 1 to day 7. The sponsor also looked at the short-term (hour to hour) effects of celecoxib and naproxen administration. In data not shown, there were no significant and clinically consistent effects detected.

(b)(4) APPEARS THIS WAY ON ORIGINAL

4.3.12.2d Analyses of Study 036 Trial Results

Table 4.3.12.2d.9 Effect of celecoxib and naproxen on creatinine clearance in study 036[a].

	Placebo N=23	Celecoxib 200 BID N=22	Naproxen 500 BID N=26
PRE-DOSE DAY ONE **Baseline (60 mins Predose)**			
Mean±SD	78.3±49	85.5±65	81.9±37
Range	(b)(4)		
PRE-DOSE DAY ONE **Baseline (30 mins Predose)**			
Mean±SD	61.9±31	65.1±31	62.3±17
Range	(b)(4)		
PRE-DOSE DAY ONE **Baseline (0 mins Predose)**			
Mean±SD	54.1±21	53.5±26	56.7±25
Range	(b)(4)		
PRE-DOSE DAY SEVEN **Baseline (60 mins Predose)**			
Mean±SD	73.9±36	66.0±36	69.6±34
Range	(b)(4)		
PRE-DOSE DAY SEVEN **Baseline (30 mins Predose)**			
Mean±SD	63.9±39	63.7±25	62.0±28
Range	14 to 168	24 to 113	10 to 135
PRE-DOSE DAY SEVEN **Baseline (0 mins Predose)**			
Mean±SD	58.2±28	60.4±29	59.0±25
Range	17 to 130	6 to 142	15 to 123
DIFFERENCE FROM DAY 7 TO PRE-DOSE DAY 1[b]			
Mean±SD	-9.6±41	-8.0±33	-10.3±29
Range	(b)(4)		
P-value[c]	0.289	0.280	0.086

a. Data from NDA volume 1.139, tables 16 and 17.
b. Data from Pre-dose Day 1 and Day 7 (0 – 1 hour postdose).
c. Using paired T-test, per the sponsor, using average of pre-dose values on Days 1 and 30 minute post-dose Day 7.

7. Safety and pharmacokinetics of celecoxib in subjects with stable chronic renal insufficiency.

The reader is referred to the pharmacologist's review for the examination of the pharmacokinetics of celecoxib.

4.3.13 Safety Outcomes

The adverse events, serious adverse events, and subject discontinuations are included in sections 8.1 and 8.2.

The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown below.

Table 4.3.13.1 Summary of subjects entered into study 036[a].

	Placebo	Celecoxib 200 BID	Naproxen 500 BID
Entered	25	23	27
Completed	23 (92%)	22 (96%)	26 (96%)
Discontinued: Total	2 (8%)	1 (4%)	1 (4%)
Protocol Non-compliance	0 (0%)	1 (4%)	0 (0%)
AEs	2 (8%)	0 (0%)	1 (4%)
Other	0 (0%)	0 (0%)	0 (0%)
Deaths	0 (0%)	0 (0%)	0 (0%)
Serious Adverse Events	0 (0%)	0 (0%)	0 (0%)
Adverse Events[b]	11 (44%)	9 (39%)	15 (56%)

a. Data from NDA volume 1.139, table 3 and table 25.
b. Counts all subjects who had at least one AE.

4.3.13.1 Comparisons of Defined Safety Endpoints

Due to the small sample size, no formal comparisons are performed. The adverse events are included in the overall safety analysis in section 8.1.

4.3.13.2 Comments on Specific Safety Parameters

Deaths

There were no deaths during the study.

Serious Adverse Events

There were no Serious Adverse Events reported during the study.

Discontinuations due to Adverse Events

Three patients withdrew from the study due to at least one adverse event: 2 (8%) placebo patients and 1 (4%) naproxen 500 mg BID patient. One placebo patient (0004-0051) withdrew from the study due to tinnitus, headache, and asthenia. One placebo patient (0007-0084) withdrew from the study due to confusion. One naproxen 500 mg BID patient (0007-0139) withdrew from the study due to urinary retention.

4.3.14 Study 036 Efficacy Summary

This study investigated the short-term effects of celecoxib and naproxen on several parameters of renal function and on the excretion of prostaglandins. The population studied were otherwise healthy individuals with stable, chronic renal insufficiency.

1. After 6 days, no effect of naproxen or celecoxib on GFR was detected (table 4.3.12.2d.1).
2. After 6 days, both celecoxib and naproxen inhibited urinary PGE2 excretion. Due to wide patient variability, the effect of celecoxib was non-significant (table 4.3.12.2d.2).
3. After 6 days, both celecoxib and naproxen significantly inhibited urinary 6-keto-PGF1-alpha excretion (table 4.3.12.2d.3). There was no significant difference between the effects of celecoxib and naproxen.
4. After 6 days, both celecoxib and naproxen significantly decreased urinary 11-dehydro-thromboxane A2 excretion. With wide subject variability, only the naproxen effect achieved nominal significance (table 4.3.12.2d.4).
5. Naproxen caused an immediate and sustained decrease in serum thromboxane levels (table 4.3.12.2d.5). Celecoxib had no significant effect on serum thromboxane levels.
6. Between days one and day seven, serum renin activity fell in the naproxen group, but rose slightly in both the celecoxib and placebo groups. These changes were non-significant (table 4.3.12.2d.6).
7. Regarding the excretion of sodium and potassium, both tended to rise between days one and 7 in both celecoxib and naproxen-treated subjects.
8. Broad variability complicates interpretation of the GFR results (see table 4.3.12.2d.9). There was no trend towards any consistent effect.

4.3.15 Study 036 Safety Summary

1. There were no deaths and no Serious Adverse Event.
2. There were no incidences of acute renal failure.

4.3.16 Study 036 Reviewer's Conclusions

With regard to efficacy, this trial in subjects with stable, mild, renal insufficiency demonstrates that both naproxen and celecoxib inhibit the excretion of urinary prostaglandins (PGE_2, 6-keto-PGF_1) and thromboxanes (urinary 11-dehydro-thromboxane A_2). Naproxen also appears to decrease serum thromboxane levels. Both celecoxib and naproxen tended to increase sodium and potassium-excretion slightly. No significant effects of either naproxen or celecoxib on GFR were detected, in part due to wide subject variability.

As regards safety, the trial is underpowered to comment on the occurrence of common renal adverse events. No unexpected toxicities were detected.

5.0 to 5.2 Integrated Renal and Cardiac Safety Review for Celecoxib

The safety review is broken into three logical sections:

5.0 Methodologies used for Safety Review

5.1 Background Database for Safety Review

5.2 Summary of Safety Review

5.0 Methodologies Used for Renal and Cardiac Safety Review

5.0.1 Subsections of the Integrated Safety Review and Preliminary Comments

Section 4.0 will use the following outline:

1) Source materials for the safety review, including the numbers of subjects exposed in each of the treatment groups, along the extent of exposure;

2) General methodologies used to elicit adverse events within the database;

3) Specific search strategies used in the celecoxib database. This will include a discussion of the sponsor's decision to split the subjects receiving heparin into two groups for purposes of safety event comparison.

5.0.2 Source Materials and Methods for the Renal/ Cardiac Safety Review

The celecoxib NDA database includes a total of 29 clinical pharmacology and 22 phase II/III clinical efficacy trials. Of these, 13 clinical trials were performed to compare celecoxib with other NSAIDs. Three of these latter studies focused on the renal effects of celecoxib: study 010 (Renal effects in the elderly); study 033 (Na^+/volume depletion and renal effects); and study 036 (Renal effects in chronic renal insufficiency). Detailed reviews of these three trials can be found elsewhere in this review/ consultation. Other individuals reviewed the remainder of the studies, and the reader is referred to those reviews for details on their efficacy results.

The database primarily used for the celecoxib renal/ cardiac safety review is drawn from the studies in OA and RA listed below. Less attention will be paid in this review to the data available from short-term administration of celecoxib in the post-surgical and dental pain trials. Where relevant the short-term database, including the surgical/ dental studies) will be specifically referred to. Additionally, the safety portions of the three 'renal' studies were reviewed individually above. Any pertinent findings from those safety reviews will be integrated into the discussion of individual adverse events in the relevant sections below.

No information from the long-term safety update was available for this review.

The next table summarizes the trials that will be emphasized for purposes of this review.

Table 5.0.2.1 Celecoxib phase II-III efficacy studies for OA and RA[a].

Study # /Duration	Short Title of Study	Included in N.A. Safety Database for Renal ISS[b]	Included in N.A. Controlled Trials[c]
020/ 12 weeks	Pivotal efficacy in knee OA	X	X
021/ 12 weeks	Pivotal efficacy/ UGI safety in knee OA	X	X
054/ 12 weeks	Pivotal efficacy in hip OA	X	X
060/ 6 weeks	Qday vs. BID efficacy	X	
087/ 6 weeks	QDay vs. BID efficacy	X	
013/ 2 weeks	Pilot OA efficacy	X	
047/ 4 weeks	Dose Ranging OA efficacy	X	
042/	International OA efficacy		
062/ 12 weeks	UGI safety vs. naproxen in OA & RA	X	
071/ 12 weeks	UGI safety vs. diclofenac and ibuprofen in OA & RA	X	
024	Long-term safety in OA & RA		
022/ 12 weeks	Pivotal efficacy/ UGI safety in RA	X	X
023/ 12 weeks	Pivotal efficacy in RA	X	X
012/ 4 weeks	Pilot RA efficacy	X	
041	International RA efficacy		
062/ 12 weeks	UGI safety vs. naproxen in OA & RA	X	
071/ 12 weeks	UGI safety vs. diclofenac and ibuprofen in OA and RA	X	
024	Long-term safety in OA and RA		

a. Data from NDA volume 1.3, table 2 and 125.

b. Database used for the sponsor's assessment of renal adverse event rates in the celecoxib database (NDA table 31.3.1).

c. Database used for the sponsor's assessment of laboratory changes in the controlled arthritis group (NDA table 25.1.1).

5.0.3 Extent of Subject Exposure to Study Drug

The dose and duration of exposure to celecoxib was discussed in section 3.1.1 above. Two of the summary tables from that section are included below, showing the numbers of subjects exposed to a given dose and time of celecoxib administration.

Dose and Duration Exposure to Celecoxib

As discussed above, the chronic exposure data comes from the trials in osteoarthritis (OA) or rheumatoid arthritis (RA). This will be the database used primarily for the assessment of renal and cardiac safety. The table below summarizes the duration of patient exposure in the OA/ RA database, broken into three categories: 0-6 weeks; 6 weeks to 6 months; and greater than 6 months. Note that there are very few subjects who received celecoxib with long-term (>180 days) exposure to celecoxib in a controlled trial (n=39). A larger number received celecoxib in open-label trials for >180 days (n=1809). This absence of long-term controlled data will limit the detection of AEs resulting from chronic exposure to celecoxib.

Table 5.0.3.1 (from table 3.1.3.2) Exposure to celecoxib, arranged by time-interval and dose in the NDA 20-998 OA/ RA database[a].

	25-50 mg	100 mg	200 mg	300 mg	400 mg	Total[b]
OR-RA Controlled Trials						
1-42 days	462	888	818	0	308	2476
32-180 days	481	1237	1836	0	307	3861
>180 days	0	0	39	0	0	39
OA-RA Uncontrolled (Open-Label) Trials						
1-42 days	110	1689	1527	768	200	4294
32-180 days	310	970	1509	451	489	3729
>180 days	0	236	941	222	410	1809
Total	1363	5020	6670	1441	1714	16208

a. Data from NDA 20-998, vol. 1.426, Table 3.4

b. There were 18 additional patients who received other doses (i.e., 200 mg in am, 300 mg in pm). These are included in the safety review but not this table.

The sponsor also summarized exposure to celecoxib in patient-years of exposure for all subjects in the arthritis trials through the NDA cutoff date of 11.21.97. The results are shown below.

Table 5.0.3.2 Duration of OA/ RA patient exposure to celecoxib, arranged by patient-years and dose, in the NDA 20-998 database[a].

	50 mg	100 mg	200 mg qD	200 mg BID	300 mg	400 mg	Any Dose[b]
OR-RA Controlled Trials	116	289	47	466	0	87	1020
OA-RA Uncontrolled (Open-Label) Trials	75	518	0	1271	340	465	2672
OA-RA Controlled & Uncontrolled Trials	117	680	47	1567	340	499	3267

a. Data from NDA 20-998, Integrated Summary of Safety, Table 4.3. Patients are counted only once per treatment group.

b. There were 18 additional patients who received other doses (i.e., 200 mg in am, 300 mg in PM). These are included in the safety review but not this table.

As discussed above, a subset of the OA/RA trials was used to construct the renal safety database prepared by the sponsor. In addition, a smaller # of the individuals were used for the detection of laboratory abnormalities (from the North American 12-week Arthritis Trials). The numbers of subjects for these two comparisons are listed below.

Table 5.0.3.3 Number of subjects in relevant subsets of the OA/ RA database for NDA 20-998[c].

Subset	Placebo	50 mg	100 mg	200 mg BID	400 mg BID	Active Control
12-Week N.A. Arthritis Trials[b]	1080	658	1099	1087	419	1071
Renal Adverse Events Safety Database[a]	1864	690	1779	1914	615	2098

a. Data from NDA 20-998, Renal Integrated Summary of Safety, Table 31.3.1. Includes studies 012, 013, 020, 021, 022, 023, 047, 054, 060, 062, 071, and 087. Additional subjects who received 25-50 mg are not shown in this table.

b. Data from NDA 20-998, Integrated Summary of Safety, Table 2.6. Includes studies 020, 021, 022, 023, and 054.

c. In many cases, the actual number of measurements available for a given measurement, especially a given laboratory measurement, is considerably less then the maximal number shown. See reviews of individual lab data for details.

5.0.4 General Methodologies Used for Safety Review

This section details the examination of AEs in the celecoxib safety database, with exclusive emphasis on the renal and cardiac AEs. In general, this was accomplished by examination of data from the Phase II-III trials, comparing the incidence of a given AE in the control group (either placebo or active control) with the group receiving celecoxib. Wherever possible, all AEs potentially linked to the administration of celecoxib are further examined for dose-, time-, sex-, age-, race-dependency. These examinations will be complicated by the different regimens employed in each of the trials for both the dose and duration of celecoxib. Due to time constraints, the majority of the datasets examined have been prepared by the sponsor, and no independent confirmation of their accuracy by this reviewer has been performed. Any primary analysis performed by FDA reviewers will be identified as such. Time constraints have also limited the examination of the individual Case Report Forms by this reviewer.

The time-dependency of an AE will be examined both in terms of the time of onset of a given AE, as well as the duration or severity of a given AE. When examining the association of drug administration to a given AE, increased significance will be given to AEs that occur during or shortly after study drug administration. For example, an AE that occurs 10 days after the end of celecoxib administration may be less likely to be related to drug administration than one that occurs during use of celecoxib.

5.0.4.1 Approach of the Sponsor to Eliciting Deaths and Serious Adverse Events

In the celecoxib NDA, an adverse experience (AE) was considered serious Adverse Events if it was fatal, life-threatening, permanently disabling, requiring prolonged hospitalization, was a congenital anomaly, a cancer, or an overdose.

Whether or not unexpected or considered to be associated with the use of the drug, were communicated to Searle or its designee immediately upon discovery of the event. The Searle monitor or designee then advised the Investigator regarding the nature of any further information or documentation that was required. The Investigator was instructed to promptly inform the Institutional Review Board of any adverse events that were considered to be serious and unexpected, and possibly related to the study drug.

Investigators were instructed to follow up all serious adverse events with appropriate medical management until they resolved.

Certain serious adverse events may not be reflected in the programmed tables or listings because, per protocol, they are not recorded in the clinical database. These include:

1. Events that occurred after a patient discontinued receiving study medication;

2. Events that were directly related to arthritis signs or symptoms that occurred in any study of arthritis patients. Investigators were instructed not to record such events as adverse events, since information related to signs and symptoms of arthritis was collected in the efficacy assessments. However, any such events that were serious were handled the same as any serious adverse event, and so narratives of these events are found in the relevant appendices.

3. Events occurring in the long-term open label trial between 11.21.97, and 5.1.98. The clinical database for this study includes only data from visits completed through 11.21.97. Therefore, serious adverse events occurring between this date and 5.1.98 are included in the appendix of MedWatch forms but not in the tables or listings.

5.0.4.2 Approach to Eliciting Adverse Events

1. General

Patients were evaluated at study visits, when they were assessed for adverse signs and symptoms that they had had since their last visit. All data on each treatment-emergent adverse event were recorded onto a case report form, along with the Investigator's opinions of :

1. whether there was a reasonable possibility that the event may have been caused by the drug (none, uncertain, or probable), and

2. the severity of the event: mild (causing no limitation of usual activities), moderate (causing some limitation of usual activities), and severe (causing inability to carry out usual activities).

In all studies, investigators were instructed to provide information concerning any findings that suggested significant hazards, contraindications, side effects, or precautions pertinent to the safety of celecoxib. In addition, Investigators were informed that an adverse event could include signs or symptoms, clinically significant laboratory abnormalities, or any abnormality detected during physical examination. In the arthritis studies, patients were asked whether they had any symptoms that were not related to their arthritis. Symptoms of arthritis of the type under study in a given trial were generally not considered as adverse events, since these findings were specifically addressed in the efficacy assessments. Any arthritis-related adverse events that met the criteria for a serious event, however, were handled and are summarized in this document the same way as other serious adverse events.

5.0.4.2 Approach to Eliciting Adverse Events (cont)

A note needs to be made regarding the detection of AEs that occur as the result of chronic exposure to study drug. As shown in section 4.0.3, there is very limited controlled data from subjects exposed to celecoxib for greater than 12 weeks. The incidence of common AEs that during long-term trials (i.e., myocardial infarction, elevated blood pressure), then, will be simply impossible to determine, since no comparison group is available. Uncommon severe AEs (i.e., vasculitis, pancytopenia) may be detected as occurring in the open-label data, although their incidence will likewise be impossible to determine.

A note also needs to be made concerning the choice of celecoxib dose used for the majority of the tables below. Given that this is a safety review, the strongest potential signal for drug toxicity is likely to be in the highest dose-group. This is particularly true in the controlled trials, where the duration of exposure is limited to 4-12 weeks. For this reason, the celecoxib 400 mg dose-group will be examine, as well as the data from the proposed doses for use (100 and 200 mg). Where relevant, the safety results from the lower doses will also be included. This will be especially important for any adverse events identified as potentially dose-related.

2. Laboratory Testing

Laboratory testing was performed according to standard laboratory practice; CLIA-approved central laboratories were used whenever possible. In all North American arthritis and analgesia studies, central laboratories analyzed all clinical laboratory samples (hematology, clinical chemistry, and urinalysis). Laboratory data were transferred to the sponsor electronically and merged into the study database. In the case of laboratory data that were obtained by a laboratory without the capacity to transmit data electronically, laboratory data were typed into databases from case report forms or from laboratory reports. All laboratory values were converted to SI units upon being entered into databases. For evaluation of clinical laboratory results, upper and lower limits representing values of potential clinical relevance were determined as were cutoff values considered to represent lower and upper extremes. These upper and lower mid-range and extreme values were developed following discussion with external safety consultants. The relevant values for this renal/ cardiac safety review are shown below. Note that there is no defined value for abnormal bicarbonate, as no bicarbonate levels were measured as part of the NDA.

Table 5.0.4.2.1 Cut-offs for abnormal lab detection in the NDA database[a].

Laboratory Test	Lower Extreme	Lower Mid-Range Limit	Higher Mid-Range Limit	Higher Extreme
Serum Chemistry	(b)(4)			(b)(4)
Creatinine			176.8 µmol/L (2.0 mg/dl)	
BUN			9.3 mmol/L (28 mg/dl)	
Glucose			8.88 mmol/L	
Uric Acid			475.8 µmol/L	
Creatine Phosphokinase (CPK)			180 U/L	
Sodium			145 mmol/L	
Potassium			5.0 mmol/L	
Chloride			110 mmol/L	
Calcium			2.74 mmol/L	
Inorganic phosphorus			1.61 mmol/L	
Cholesterol (total)			6.5 mmol/L	
Urinalysis				
Protein			Trace	
Blood			Trace	
Glucose			Trace	
pH			4 8	
Specific gravity			1.030	
RBC			5/hpf	
WBC			10/hpf	
Ketones			Trace	
Urine bilirubin			Trace	

a. Data from NDA Integrated Safety Summary, text table 3.

3. Extent of Laboratory Testing, Reporting and Follow-up for Abnormal Lab Values

Laboratory safety measurements (hematology, serum chemistry, urinalysis, and miscellaneous) were performed at intervals during the clinical trials reported in this submission. Since not all patients had all laboratory tests performed, the denominator for a laboratory adverse experience varies, and is the number of patients who had that laboratory test performed. The reporting of any laboratory adverse experience was always dependent on the individual investigator's assessment of its clinical importance. Thus, laboratory values within or outside the normal range could be interpreted as adverse by one investigator and not by another.

4. Vital Signs

The sponsor also established broad limits for abnormal vital signs, including weight. These are summarized below.

Table 5.0.4.2.2 Cut-offs for abnormal lab detection in the NDA database[a].

Laboratory Test	Lower Extreme	Higher Extreme
Systolic BP	15% decrease from Baseline	15% increase from Baseline
Diastolic BP	15% decrease from Baseline	15% increase from Baseline
Pulse rate	15% decrease from Baseline	15% increase from Baseline
Body weight	5% decrease from Baseline	5% increase from Baseline

a. Data from NDA Integrated Safety Summary, text table 4.

5.0.5 Selecting the Key Adverse Event Tables for Characterizing the Adverse Event Profile

Adverse events were coded using the World Health Organization Adverse Reaction Terminology (WHOa.r.t.) dictionary. Conventions for assigning Included and Preferred Terms to certain events were adopted in order to ensure consistent coding of events among different studies and coders.

Included in this review of renal and cardiac safety will be all adverse events referable to either of those two body systems as mapped by WHO. In addition, adverse events related to the lab values listed above, as well as changes in vital signs (weight, pulse rate, blood pressure) will also be investigated.

5.0.6 Specific Search Strategies Unique to the Celecoxib Renal/ Cardiac Safety Review

This review will focus entirely on those adverse events, including deaths, SAEs and lab abnormalities, relevant to cardiac and/or renal safety.

The majority of the estimates of incidence of specific AEs will be based on the pooled data from the phase II-III studies done in OA and RA. This is based on the homogeneity of the patient population entered into those trials. The long-term open-label study will be critical in evaluating the occurrence of AEs that require longer periods of drug exposure, even though no placebo or control group is available. Time limitations will limit the exploration for drug-disease, drug-drug, and drug-demographic interactions with celecoxib as they concern renal and cardiac toxicity.

5.1 Background Database for Safety Review

For the purposes of this section, the primary analysis will compare the incidence of AEs and SAEs in the database between three groups: celecoxib alone, active control, and placebo.

In the integrated safety summary, adverse events will be examined in the following order:

1) Deaths,
2) Serious Adverse Events (SAEs),
3) Adverse Events (AEs) related to clinical findings,
4) Adverse Events related to laboratory findings and special examinations,

and 5) Subject discontinuations.

Following this, the occurrence of AEs in subjects with pre-existing renal or cardiac disease will be examined, including the safety database from the three 'Renal' trials. The datatables below have been submitted to the sponsor to allow for correction of typographical or other errors of presentation.

5.1.1 Deaths in the celecoxib safety database

Deaths will be examined first in the overall database, and then in each trial as relevant.

5.1.1.1 Integrated data on deaths in the celecoxib database

There were 26 deaths in patients who participated in studies included in the NDA. A narrative listing of all of the deaths is to be found in Appendix one of this consult (section 6.1).

A total of eight subjects who enrolled in controlled arthritis trials died. Six deaths occurred during controlled arthritis studies, and two following discontinuation of study drug. Four of the individuals in the controlled arthritis group who died received celecoxib, while four received active control drug. Based on review of the individual case report forms and summaries by the medical reviewer, and discussion with the sponsor, the individuals in bold letters died of cardiovascular disease.

Table 5.1.1.1.1 Deaths during controlled trials in the NDA 20-998 database[a].

Subject #	Age/ Sex	Treatment	Duration of Tx	Cause of Death
Deaths During Study Drug Administration				
071-US0382-65811310	78/M	Ibuprofen 800 mg TID	29	Obstructive pulmonary disease
062-US0117-46761235	**68/M**	**Naproxen 500 mg BID**	**63**	**Brain-stem infarct**
021-US0191-1334	67/M	Naproxen 500 mg BID	47	Pulmonary embolus
071-US0333-46521451	**53/F**	**Diclofenac 75 mg BID**	**1**	**Hypertensive cardiovascular disease**
041-BE0002-0010	70/M	Celecoxib 200 mg BID	81	Gallbladder carcinoma with liver metastasis
087-US0021-0182	**56/M**	**Celecoxib 200 mg QD**	**30**	**Arteriosclerotic cardiovascular disease**
Deaths After Study Drug Discontinuation				
020-US0052-0683	62/F	Celecoxib 100 mg BID	26/ 54	Pulmonary carcinoma
020-US0033-0768	**80/F**	**Celecoxib 200 mg BID**	**6/45**	**MI**

a. Data from Integrated Safety Summary, Text Table 67. Table shows all deaths from controlled trials, including those that occurred after the study drug was discontinued. For those two subjects, the # of days after drug discontinuation for the death is shown after the day of death.

Ten deaths occurred during the long-term open-label study prior to the database cutoff date (November 21, 1997), and are summarized below. The duration of treatment ranged from 15 to 273 days, with a final regimen of 200 mg BID for four patients, 300 mg BID for two patients and 400 mg BID for four patients. The subjects in bold letters (9/10, 90%) died of cardiovascular disease.

Table 5.1.1.1.2 Deaths during the long-term open-label trial prior to database cutoff date of Nov. 21, 1997[a].

Subject #	Age/ Sex	Treatment	Day of Death	Cause of Death
Celecoxib 200 mg				
024-US0023--0230020	**76/M**	**Celecoxib 200 mg BID**	**45**	**MI, cardiac failure**
024-US0053--0530001	**80/M**	**Celecoxib 200 mg BID**	**159**	**Massive coronary**
024-US0058--0580018	**59/M**	**Celecoxib 200 mg BID**	**246**	**Ischemic heart disease**
Celecoxib 300 mg				
024-US0052--0520043	**83/F**	**Celecoxib 300 mg BID**	**193**	**Coronary thrombosis**
024-US0121--1210052	**52/M**	**Celecoxib 300 mg BID**	**114**	**MI**
024-US0066--0660004	60/M	Celecoxib 400 mg BID	155	Adenocarcinoma
Celecoxib 400 mg				
024-US0073--0730060	**84/F**	**Celecoxib 400 mg BID**	**243**	**Respiratory failure, CHF**
024-US0024--0240004	**58/M**	**Celecoxib 400 mg BID**	**273**	**MI**
024-US0001-0010053	**65/F**	**Celecoxib 400 mg BID**	**196**	**Myocardial rupture post-MI**
024-CA0139--139009	**57/F**	**Celecoxib 200 mg BID**	**15**	**Subarachnoid hemorrhage**

a. Data from Integrated Safety Summary, Text Table 66.

There were also five deaths in the long-term open label study between the database cutoff date and May 1, 1998. All were due to cardiovascular disease (and are shown in bold letters).

Table 5.1.1.1.3 Deaths during the long-term open label trial after cutoff Date of Nov. 21, 1997[a].

Subject #	Age/ Sex	Treatment	Day of Death	Cause of Death
024-US0116-1160042	**78/F**	**Celecoxib 200 mg BID**	**88**	**Aortic Aneurysm**
024-US0001-0010076	**74/M**	**Celecoxib 400 mg BID**	**336**	**Heart block**
024-US0024-0240024	**71/M**	**Celecoxib 400 mg BID**	**32**	**Coronary artery disorder**
024-US0073-0730189	**71/F**	**Celecoxib 400 mg BID**	**37**	**MI**
024-US0110-1100006	**61/F**	**Celecoxib 400 mg BID**	**471**	**MI**

a. Data from Integrated Safety Summary, Text Table 67.

Finally, there were five deaths that occurred more than 28 days after last dose in any study reported in this New Drug Application (note that the two patients in the 020 trial are included in table 5.1.1.1 above. Two of these patients died after participation in trial 020 and three died following participation in Study 024 (long-term, open-label trial). Of the five celecoxib subjects in this group, two died of cardiovascular disease (40%).

Table 5.1.1.1.4 Deaths that occurred more than 28 days after last dose[a].

Subject #	Age/Sex	Treatment	Day of Death	Days after Last Dose	Cause of Death
020-US0052-0683	62/F	Celecoxib 100 mg BID	6	54	Pulmonary carcinoma
020-US0033-0768	**80/F**	**Celecoxib 200 mg BID**		**45**	**MI**
024-CA0087-0870100	66/M	Celecoxib 200 mg BID	73	29	Sepsis, pneumonitis
024-US0042- 0420004	77/F	Celecoxib 200 mg BID	11	36	Pulmonary carcinoma
024-US0027- 0270004	**66/M**	**Celecoxib 400 mg BID**	**34**		**Anterior MI**

a. Data from Integrated Safety Summary, Text Tables 66 and 68.

5.1.1.2 Mortality Rate due to Cardiovascular Disease and for Total Mortality

1. Total Mortality

Depending on the population used for the denominator, mortality can be calculated in two ways using the information from the celecoxib database, summarized above.

The first way uses the number of subjects exposed to the drug in each treatment group, independent of the duration of that exposure.

Table 5.1.1.2.1 Calculation of crude mortality incidence in deaths per patients exposed in NDA 20-998[a].

Population	Number of Deaths	Number of Exposed Subjects	Crude Mortality Incidence
Controlled N.A. OA/RA Trials			
Deaths during trial			
Placebo	0	1864	0%
Celecoxib	2	6376[e]	0.03%
Active Control	4	2768	0.14%
All known deaths[b]			
Placebo	0	1864	0%
Celecoxib	4	6376[e]	0.06%
Active Control	4	2768	0.14%
Long-term, Open-label Trial			
Deaths before cut-off date	10	5155	0.19%
Known deaths during celecoxib use	15[d]	5155	0.29%
All known deaths[c]	18	5155	0.35%

a. Data from Integrated Safety Summary, including Text Tables 65-68 and Summary table 2.9. Confirmed with the sponsor.

b. Includes one death in the active control group and two deaths in the celecoxib group after trial completion. These deaths occurred >28 days after last dose of study medication.

c. For all patients who received celecoxib. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date for the ongoing trial (11.21.97). Also includes three deaths that occurred >28 days after last reported use of celecoxib (see tables 5.1.1.1 to 5.1.1.4).

d. Includes five deaths that occurred during celecoxib administration, reported after cut-off date (11.21.97).

e. Number equals the total number of individual patients in the OA and RA trials (4151 and 2086, see table 3.1.2.1).

It is also fruitful to calculate mortality using the data on patient-years of exposure as the denominator. These calculations are in the table below.

Table 5.1.1.2.2 Calculation of mortality rate in deaths per patient-years of exposure in NDA 20-998[a].

Population	Number of Deaths	Patient-yrs of Exposure[e]	Mortality Rate
Controlled N.A. OA/RA Trials			
Deaths during trial			
Placebo	0	208	0.00%
Celecoxib	2	1020	0.19%
Active Control	4	535	0.75%
All known deaths[b]			
Placebo	0	208	0.00%
Celecoxib	4	1020	0.39%
Active Control	4	535	0.74%
Long-term, Open-label Trial			
Deaths before cut-off date	10	2672	0.37%
Known deaths during celecoxib use	15[d]	4274	0.35%
All known deaths[c]	18	4274	0.42%

a. Data from Integrated Safety Summary, including Text Tables 65-68.

b. Includes one death in the active control group and two deaths in the celecoxib group after trial completion. These deaths occurred >28 days after last dose of study medication.

c. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date for the ongoing trial (11.21.97). Also includes three deaths that occurred >28 days after last reported use of celecoxib (see tables 5.1.1.1 to 5.1.1.4).

d. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date for the ongoing trial (11.21.97).

e. Data from table 3.1.3.3 and from sponsor at request of reviewer.

2. Cardiovascular Mortality

In similar fashion, the mortality rate due to cardiovascular disease can be calculated. The deaths attributed to cardiovascular disease were highlighted in the tables of deaths above, as determined by review of the sponsor-generated narrative summaries and the case report forms.

Cardiovascular mortality per patients exposed

Table 5.1.1.2.3 Calculation of crude cardiovascular mortality incidence in deaths per patients exposed in NDA 20-998[a].

Population	# of Deaths	# of Exposed Subjects	Mortality Incidence
Controlled N.A. OA/RA Trials			
Cardiac deaths during trial			
Placebo	0	1864	0.00%
Celecoxib	1	6376[e]	0.02%
Active Control	2	2768	0.07%
All known cardiac deaths[b]			
Placebo	0	1864	0.00%
Celecoxib	2	6376[e]	0.03%
Active Control	2	2768	0.07%
Long-term, Open-label Trial			
Cardiac deaths before cut-off date	9	5155	0.17%
Known deaths during celecoxib use	14[d]	5155	0.27%
All known cardiac deaths[c]	15	5155	0.29%

a. Data from Integrated Safety Summary, including Text Tables 65-68.

b. Includes one death in the active control group and two deaths in the celecoxib group after trial completion. These deaths occurred >28 days after last dose of study medication.

c. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date for the ongoing trial (11.21.97). Also includes three deaths that occurred >28 days after last reported use of celecoxib (see tables 5.1.1.1 to 5.1.1.4).

d. Includes five deaths that occurred during celecoxib administration, reported after cut-off date (11.21.97).

e. Number equals the total number of individual patients in the OA and RA trials (4151 and 2086, see table 3.1.2.1).

Cardiovascular mortality in deaths per patient-years of exposure

It is also fruitful to calculate mortality using the data on patient-years of exposure as the denominator. These calculations are in the table below.

Table 5.1.1.2.4 Calculation of cardiovascular mortality rate in deaths per patient-years of exposure[a].

Population	# of Deaths	Patient-years of Exposure[e]	Mortality Rate
Controlled N.A. OA/RA Trials			
Cardiac deaths during trial			
Placebo	0	208	0.00%
Celecoxib	1	1020	0.10%
Active Control	2	535	0.37%
All Known Cardiac Deaths[b]			
Placebo	0	208	0.00%
Celecoxib	2	1020	0.20%
Active Control	2	535	0.37%
Long-term, Open-label Trial			
Cardiac deaths before cut-off date	9	2672	0.33%
Known deaths during celecoxib use	14[d]	4274	0.33%
All known cardiac deaths[c]	15	4274	0.35%

a. Data from Integrated Safety Summary, including Text Tables 65-68.

b. Includes one death in the active control group and two deaths in the celecoxib group after trial completion. These deaths occurred >28 days after last dose of study medication.

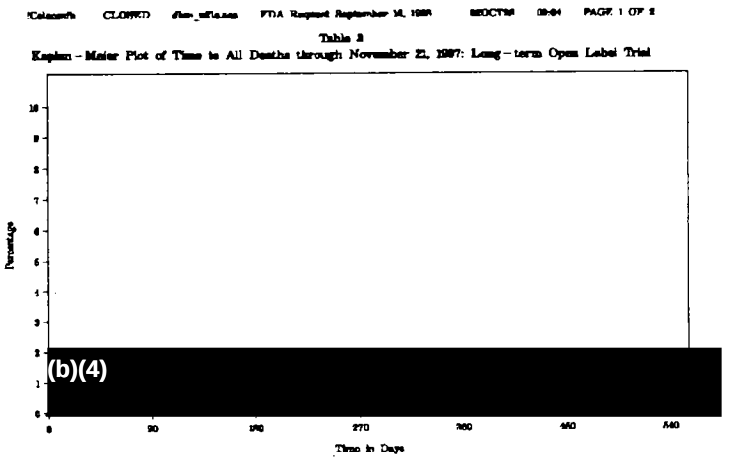
c. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date for the ongoing trial (11.21.97). Also includes three deaths that occurred >28 days after last reported use of celecoxib (see tables 5.1.1.1 to 5.1.1.4).

d. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date (11.21.97).

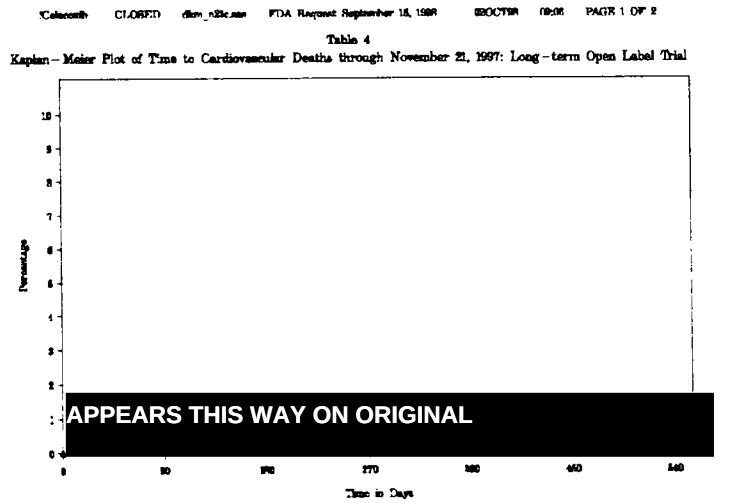
e. Data from table 3.1.3.3 and from sponsor at request of reviewer.

At this reviewer's request, the sponsor obtained Kaplan-Meier curves for both all-cause and cardiovascular mortality. These curves allow the reader to look at the relationship between duration of exposure to drug and time of death, to look for clustering of deaths, which might suggest a common etiology of death related to drug-exposure. Given the small number of deaths in the controlled-trial 12-week database, those curves are not enlightening and are not shown here.

The first curve below shows the survival analysis for all-cause mortality from the long-term trial, through November 22, 1997.



The next curve shows the Kaplan-Meier plot of time to death for the cardiovascular deaths in the open-label trial. Deaths were identified as cardiovascular by the Medical Reviewer through review of case report forms and discussion with sponsor.



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Finally, the sponsor derived a Kaplan-Meier plot of all known and cardiovascular deaths, including those that occurred more than 28 days after discontinuation of celecoxib. These curves, like those above, show a broad scatter of time to death relative to the duration of exposure to celecoxib.

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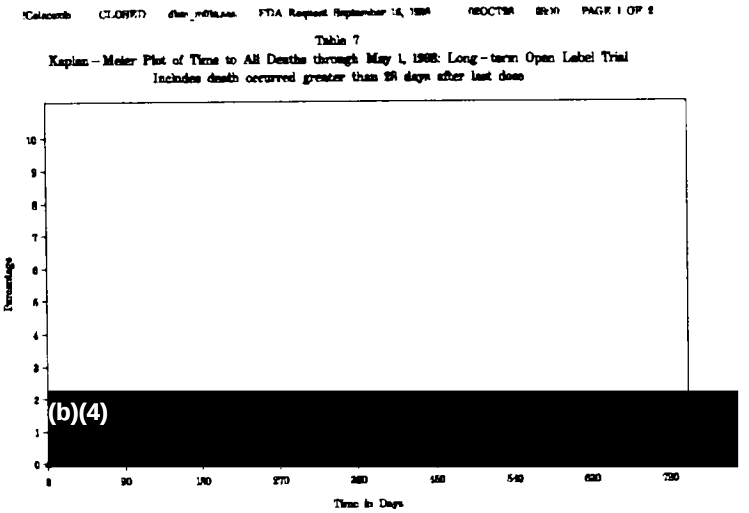

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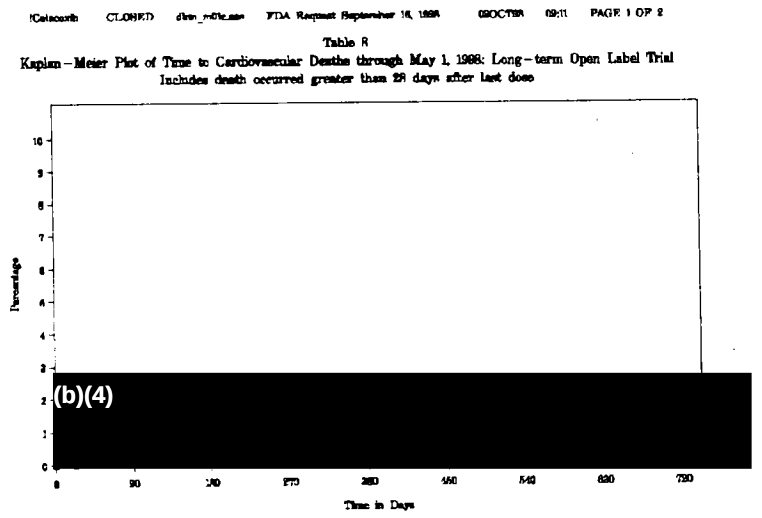

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The Kaplan-Meier plots can also be used to derive cumulative incidence rates for all-cause and cardiovascular mortality (chosen at 24 and 52 weeks). The first table comes from the controlled-trial OA/RA database.

Table 5.1.1.2.5 Kaplan-Meier estimates for cumulative incidence rates for all mortality in the North American OA/ RA trials[a].

Controlled Studies (24 weeks)	*All-Cause Deaths (n, %)*	Cardiovascular Deaths (n, %)
Deaths ≤28 days after last dose of study drug		
Placebo	0 (0%)	0 (0%)
Celecoxib	2 (0.38)	1 (0.02%)
Active Control	4 (0.26%)	2 (0.12%)
All deaths		
Placebo	0 (0%)	0 (0%)
Celecoxib	4 (0.45%)	2 (0.05%)
Active Control	4 (0.22%	2 (0.10%)

a. Data from sponsor-derived plots.

The next table comes from the long-term trials, using various cut-offs for inclusion.

Table 5.1.1.2.6 Kaplan-Meier estimates for cumulative incidence rates for cardiovascular mortality in the open-label, long-term trial (024)[a].

Long-term Open-Label Study(52 wks)	All-Cause Deaths (n, %)	Cardiovascular Deaths (n, %)
Deaths ≤28 days after last dose of study drug		
As of 11.21.97	10 (0.43%)	9 (0.39%)
As of 5.1.98	15 (0.38%)	14 (0.35%)
All deaths		
As of 5.1.98	18 (0.41%)	14 (0.35%)

a. Data from sponsor-derived plots.

Finally, it is possible to look at the mortality rate per patient-yr of exposure in the long-term trial, arranged by highest dose of celecoxib used by each patient prior to death. The small numbers of patients obviously make interpretation of such calculated rates difficult. Since all of the patients in this group died of cardiovascular causes, the total mortality and the cardiovascular mortality rates are the same.

Table 5.1.1.2.7 Calculation of cardiovascular mortality rates in deaths per patient-years of exposure, arranged according to highest dose of celecoxib received, from the long-term trial[a,b].

Celecoxib Dose	Number of Deaths	Patient-years of Exposure[d]	Crude Mortality Rate[c]
100 mg	0	519	0%
200 mg	4	1271	0.31%
300 mg	2	340	0.59%
400 mg	3	465	0.64%

a. Data from Integrated Safety Summary, including Text Tables 65-68.
b. Data shown for deaths that occurred prior to cut-off date 11.21.97.
c. Mortality (for both total and cardiovascular deaths) in deaths/pt-yrs (x100).
d. Data from ISS, Appendix table 4.3.

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5.1.2 Other Serious Adverse Events (SAEs) in the Phase II-III Safety Database

The SAEs in the database were analyzed in several different ways by the sponsor. For the discussion below, the initial examination will be of the combined North American OA/RA trials. Next, the SAEs reported during the long-term, open-label trials will be summarized. Finally, the SAEs collected by the sponsor and felt to be related to renal AEs will be summarized.

Table 5.1.2.1 Serious cardiac and renal adverse events collected in the North American Arthritis trial database[a].

Body System/ SAE	Placebo N=1864	Celecoxib 25-400 mg N=5083	Active Controls N=2098
Total # with SAEs	30 (1.6%)	75 (1.5%)	39 (1.9%)
Body as a whole	3 (0.2%)	9 (0.2%)	5 (0.2%)
Sudden Death	0 (0%)	0 (0%)	1 (<0.1%)
Chest pain	0 (0%)	3 (<0.1%)	0 (0%)
Cardiovascular System	1 (<0.1%)	5 (0.1%)	2 (0.1%)
Angina, unstable	0 (0%)	1 (<0.1%)	1 (<0.1%)
Heart failure	1 (<0.1%)	3 (<0.1%)	0 (0%)
Myocardial infarction	2 (0.1%)	8 (0.1%)	2 (0.1%)
Rhythm Disturbances[b]	1 (<0.1%)	5 (0.1%)	2 (0.1%)
Hypertension[c]	0 (0%)	3 (<0.1%)	0 (0%)
Hypotension	0 (0%)	0 (0%)	1 (<0.1%)
Urinary System	2 (0.1%)	3 (<0.1%)	2 (0.1%)
Renal Failure	0 (0%)	0 (0%)	0 (0%)

a. Data from NDA Integrated Safety Summary, Appendix Table 22.1, and electronic datasets. Numbers shown as individual subjects. Note that in some cases, a subject may have had more than one serious adverse event in the same category, which is not captured here.

b. Includes the following terms: arrhythmia; atrial arrhythmia; atrial fibrillation; heart block; palpitation; and supraventricular tachycardia.

c. Includes hypertension and aggravated hypertension.

The next table shows the incidence of relevant serious adverse events that occurred in the long-term, open-label celecoxib trials.

Table 5.1.2.2 Serious renal and cardiac adverse events collected in long-term, open-label database[a].

Body System/ SAE	Combined N=4499
Total # with SAEs	244 (5.4%%)
Body as a Whole	
Death	1 (<0.1%)
Chest pain	6 (0.1%)
Cardiovascular System	
Angina, unstable	5 (0.1%)
Heart failure (left or right)	6 (0.1%)
Cardiac Arrest	1 (<0.1%)
Myocardial infarction[b]	16 (0.4%)
Bradycardia	2 (<0.1%)
Atrial Fibrillation	4 (<0.1%)
Ventricular Fibrillation	1 (<0.1%)
Urinary System	
Renal Failure	1 (<0.1%)
Bladder Carcinoma	3 (0.1%)
Renal Calculus	2 (<0.1%)

a. Data from NDA Integrated Safety Summary, Table 22.2, and electronic datasets. Numbers shown as individual subjects. Note that in some cases, a subject may have had more than one serious adverse event in the same category, which is not captured here.

b. Includes coronary thrombosis and myocardial infarction.

The sponsor also collected those SAEs they felt potentially linked to renal disease. These are listed below. Note that several of the celecoxib events are primarily related to excess fluid retention. The relative incidence rates for the placebo, celecoxib and active control groups were 2/1864 (0.05%), 7/5083 (0.14%) and 1/2098 (0.05%). Narratives for all of the listed patients can be found Appendix two, section 10.1 of this review.

Examination of the SAEs from the International trials and from the Pain trials (not shown) revealed no unanticipated SAEs, or SAEs occurring at significantly different frequencies from those listed in the North American OA/RA trials. Time constraints prevented the reviewer from examining the Case Report Forms for each patient.

Table 5.1.2.3 Renal and Cardiac SAEs in the celecoxib database[a].

Serious Adverse Event	Patient #	Age/ Sex	Treatment	Stopped Tx?
Controlled Trials				
Aggravated hypertension	071-US0016-76132005	62/F	Celecoxib 200 mg BID	No
Aggravated Hypertension	062-US0265-54241602	40/F	Celecoxib 200 mg BID	No
Cardiac failure	021-US0113-0139	81/F	Celecoxib 200 mg BID	Yes
Cardiac failure	054-US0016-1467	66/F	Placebo	Yes
Cardiac failure	060-US0198-0214	76/M	Celecoxib 100 mg BID	Yes
Hypertension	022-US0114-0683	54/F	Celecoxib 400 mg BID	Yes
Renal calculus	022-US0114-0345	62/M	Placebo	Yes
Renal calculus	071-US0354-56553061	27/F	Celecoxib 200 mg BID	Yes
Pyelonephritis	071-US0267-77861660	51/F	Ibuprofen 800 mg BID	Yes
Uremia	047-US0033-0030	70/F	Celecoxib 400 mg BID	Yes
Long-term Open Label Trial				
Acute renal failure	024-US0149-1490002	65/M	Celecoxib 200 mg BID	Yes
Aggravated hypertension	024-US0005-0050022	71/F	Celecoxib 100 mg BID	No
Respiratory failure	024-US0006-0060001	71/M	Celecoxib 300 mg BID	Yes
Prostatic disorder	024-US0002-0020014	66/M	Celecoxib 300 mg BID	No
Hydronephrosis	024-US0074-0740011	71/F	Celecoxib 300 mg BID	Yes
Hypokalemia	024-US0013-0130009	78/F	Celecoxib 200 mg BID	No
Hyponatremia	024-US0033-0330007	72/F	Celecoxib 300 mg BID	Yes
Pyelonephritis	024-US0030-0300024	70/F	Celecoxib 200 mg BID	No
Pyelonephritis	024-US0007-0070058	55/F	Celecoxib 100 mg BID	Yes
Renal calculus	024-US0001-0010016	43/M	Celecoxib 200 mg BID	Yes
Renal calculus	024-US0009-009037	58/F	Celecoxib 200 mg BID	No
Renal colic	024-US0043-0430011	53/F	Celecoxib 100 mg BID	No

a. Data from Integrated Summary of Safety, Text Table 136.

5.1.3 Clinical Adverse Events (AEs) from the Celecoxib Safety Database

The adverse experience tables below present the percentages of subjects having at least one adverse event on treatment during the adverse experience reporting period of each trial. A subject may be counted more than once if he/she had multiple adverse experiences classified in more than one body system. However, a given patient is counted only once in the overall total and once in any particular body system, regardless of how many clinical adverse experiences were reported in that body system. Similarly, a subject who reported multiple occurrences of the same adverse event appears only once for that particular adverse event.

The list of adverse events is, again, focused on cardiovascular and renal AEs. For some categories, this reviewer has combined more than one type of AEs (in particular, the AEs relating to edema). The shaded boxes represents AEs where there is ≥2X difference between the celecoxib groups and either of the placebo or active control groups, and where the minimal incidence rate was 0.1%. The celecoxib data are presented in two columns. First, the incidence of AEs from all subjects who received celecoxib in the database. The data focusing on the AEs in the 100-200 mg dose group are also presented. Examination of the AEs from the International trials and from the Pain trials revealed no unanticipated AEs, or AEs occurring at significantly different frequencies from those listed in the North American OA/RA trials below. The incidence of peripheral edema was significantly greater in the celecoxib when compared with placebo (p=0.007).

Table 5.1.3.1 Adverse events in the North American Arthritis trials of celecoxib from NDA 20-998[a]. Part one: Cardiovascular AEs.

Clinical AE	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=4146	Active Controls N=2098
Subjects with an AE	1018 (55%)	3451 (63%)	2503 (60%)	1399 (67%)
Body as a Whole				
Chest Pain	14 (0.8%)	40 (0.7%)	33 (0.9%)	16 (0.8%)
Edema, Generalized	**0 (0%)**	**8 (0.14%)**	**5 (0.1%)**	**10 (0.5%)**
Edema, Facial	8 (0.4%)	23 (0.4%)	17 (0.4%)	5 (0.2%)
Edema, Peripheral	**21 (1.1%)**	**124 (2.2%)**	**89 (2.1%)**	**45 (2.1%)**
Edema, Peri-orbital	0 (0%)	2 (<0.1%)	2 (<0.1%)	0 (0%)
Edema, Legs	0 (0%)	1 (<0.1%)	1 (<0.1%)	0 (0%)
Edema, All Categories	**29 (1.6%)**	**158 (2.8%)**	**114 (2.7%)**	**60 (2.8%)**
Cardiovascular System				
Sudden Death	0 (0%)	0 (0%)	0 (0%)	1 (<0.1%)
Cardiac Failure[b]	1 (<0.1%)	5 (0.1%)	4 (0.1%)	2 (0.1%)
Heart Valve Disorder	0 (0%)	4 (<0.1%)	3 (0.1%)	3 (0.1%)
Hypertension[c]	**12 (0.6%)**	**64 (1.1%)**	**55 (1.6%)**	**20 (1.0%)**
Hypotension	1 (<0.1%)	1 (<0.1%)	0 (0%)	4 (0.2%)
Hypotension, Postural	0 (0%)	2 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Syncope	2 (0.1%)	3 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Arrhythmia[d]	**2 (0.1%)**	**7 (0.1%)**	**6 (0.1%)**	**6 (0.3%)**
Atrial fibrillation	1 (<0.1%)	1 (<0.1%)	0 (0%)	1 (<0.1%)
Bradycardia	0 (0%)	0 (0%)	0 (0%)	4 (4 (0.2%)
Tachycardia[e]	**1 (<0.1%)**	**16 (0.3%)**	**9 (0.2%)**	**2 (0.1%)**
Palpitations	**1 (<0.1%)**	**22 (0.4%)**	**13 (0.3%)**	**11 (0.5%)**
Ventricular arrhythmia	0 (0%)	0 (0%)	0 (0%)	1 (<0.1%)
Myocardial, Pericardial and Valve Disorders				
Angina Pectoris[f]	5 (0.3%)	18 (0.3%)	14 (0.3%)	6 (0.3%)
Coronary Artery Disorder	2 (0.1%)	6 (0.1%)	5 (0.1%)	0 (0%)
Pericarditis	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)
Myocardial Infarction (MI)[g]	**2 (0.1%)**	**10 (0.2%)**	**9 (0.2%)**	**2 (0.1%)**
MI + Coronary Artery Disorder	**4 (0.2%)**	**16 (0.3%)**	**14 (0.3%)**	**2 (0.1%)**

a. Data from NDA Integrated Safety Summary. table 6.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

b. Includes left, right, and undifferentiated cardiac failure.

c. Includes both undifferentiated hypertension and aggravated hypertension.

d. Includes undifferentiated arrhythmia, atrial and ventricular arrhythmia.

e. Includes undifferentiated and supraventricular tachycardia.

f. Includes 'aggravated' and 'unstable' angina pectoris.

g. Includes 'Thrombosis, coronary'.

Table 5.1.3.1 (cont) Adverse events in the North American Arthritis trials of celecoxib from NDA 20-998[a] Part two: Renal AEs.

Clinical AE	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=3512	Active Controls N=2098
Renal System				
Uremia	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)
BUN Increased	1 (<0.1%)	11 (0.2%)	7 (0.2%)	2 (0.1%)
Nephritis	0 (0%)	1 (<0.1%)	1 (<0.1%)	2 (0.1%)
Renal Calculus	1 (<0.1%)	7 (0.1%)	5 (0.1%)	2 (0.1%)
Urinary Abnormalities				
Albuminuria	2 (0.1%)	15 (0.3%)	12 (0.3%)	1 (<0.1%)
Hematuria	3 (0.2%)	11 (0.2%)	7 (0.2%)	2 (0.1%)
Pyuria	2 (0.1%)	3 (<0.1%)	2 (<0.1%)	2 (0.1%)
Urinary Tract Infection	16 (0.9%)	63 (1.1%)	44 (1.1%)	27 (1.3%)
Urinary Incontinence	3 (0.2%)	5 (0.1%)	5 (0.1%)	3 (0.1%)
Metabolic Abnormalities				
Hypercalcemia	1 (<0.1%)	5 (0.1%)		1 (0.1%)
Hyperchloremia	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hyperkalemia	0 (0%)	5 (0.1%)	3 (<0.1%)	0 (0%)
Hypernatremia	0 (0%)	1 (<0.1%)	1 (<0.1%)	0 (0%)
Hyperuricemia	2 (0.1%)	6 (0.1%)	4 (0.1%)	0 (0%)
Hypocalcemia	0 (0%)	2 (<0.1%)		1 (0.1%)
Hypokalemia	8 (0.4%)	16 (0.3%)	9 (0.2%)	4 (0.2%)
Hyponatremia	4 (0.2%)	2 (<0.1%)	1 (<9.1%)	0 (0%)
Hypophosphatemia	0 (0%)	1 (<0.1%)	1 (<0.1%)	0 (0%)

a. Data from NDA Integrated Safety Summary, table 6.2 and 31.3.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

The above table of AEs draws from the short-term arthritis trials. The table below summarizes the incidence data on AEs in the long-term open-label trial. The same conventions in the previous two tables apply.

Table 5.1.3.2 Renal and cardiovascular adverse events in the long-term, open-label trial of celecoxib (024) from NDA 20-998[a] Part one: Cardiovascular AEs.

Clinical AE	Celecoxib 25-400 mg N=4499
Subjects with a clinical AE	3327 (73.9%)
Body as a Whole	
Chest Pain	70 (1.6%)
Edema, Generalized	26 (0.6%)
Edema, Facial	13 (0.3%)
Edema, Peripheral	172 (3.8%)
Edema, Tongue	4 (<0.1%)
Edema, All Categories	285 (6.3%)
Cardiovascular System	
Sudden Death	1 (<0.1%)
Cardiac Failure[b]	11 (0.2%)
Heart Valve Disorder	8 (0.2%)
Hypertension[c]	110 (2.4%)
Hypotension	4 (<0.1%)
Syncope	9 (0.2%)
Arrhythmia[d]	10 (0.2%)
Atrial fibrillation	9 (0.2%)
Bradycardia	3 (<0.1%)
Tachycardia[e]	24 (0.5%)
Palpitations	19 (0.4%)
Ventricular arrhythmia	1 (<0.1%)

Table 5.1.3.2 Adverse events in the long-term, open-label trial of celecoxib from NDA 20-998[a] Part two: Cardiac and Renal AEs.

Clinical AE	Celecoxib 25-400 mg N=4499
Myocardial, Pericardial and Valve Disorders	
Angina Pectoris[f]	35 (0.8%)
Coronary Artery Disorder	16 (0.4%)
Pericardial Effusion	1 (<0.1%)
Myocardial Infarction (MI)[g]	19 (0.4%)
MI + Coronary Artery Disorder	35 (0.8%)
Renal System	
Uremia	0 (0%)
BUN Increased	14 (0.3%)
Nephritis	1 (<0.1%)
Cystitis	45 (1.0%)
Renal Calculus	11 (0.2%)
Urinary Abnormalities	
Albuminuria	23 (0.5%)
Hematuria	23 (0.5%)
Pyuria	8 (0.2%)
Urinary Tract Infection	142 (3.2%)
Urinary Incontinence	9 (0.2%)
Metabolic Abnormalities	
Hypercalcemia	4 (<0.1%)
Hyperchloremia	2 (<0.1%)
Hyperkalemia	6 (0.1%)
Hypernatremia	2 (<0.1%)
Hyperuricemia	14 (0.3%)
Hypocalcemia	2 (<0.1%)
Hypokalemia	16 (0.4%)
Hyponatremia	3 (<0.1%)
Hypophosphatemia	0 (0%)

a. Data from NDA Integrated Safety Summary, table 6.2. The database used is from trial 024.

5.1.4 Adverse Events Related to Laboratory Findings

5.1.4.1 Standard Analyses and Explorations of Laboratory Data

Laboratory data are presented in this section in three ways: 1) incidence of extreme laboratory values; 2) comparison of mean laboratory values; and 3) shifts of laboratory values among the five categories defined by the extreme and mid-range high and low values for each laboratory test. Shown are the incidence of extreme values at any time during the trial. In this short-term database, there were relatively few extreme values.

Incidence of extreme laboratory values

The summary data below comes from the North American OA/RA trials. An examination of the labs from the smaller International trials, comparing celecoxib with active control, and from the Pain trials revealed no lab abnormalities occurring at significantly different frequencies from those below.

Table 5.1.4.1.1 Incidence of extreme renal lab values in the controlled North American Arthritis trials of celecoxib from NDA 20-998[a].

	Placebo N=1080[b]	Celecoxib 400 mg N=3250[c]	Active Controls N=1060[d]
Lab Test, Low Extreme Criteria			
Sodium <120 mmol/L	0 (0%)	0 (0%)	0 (0%)
Potassium <2 meq/	0 (0%)	0 (0%)	0 (0%)
Chloride <75 mmol/L	0 (0%)	0 (0%)	0 (0%)
Calcium <1.7 or 15% decrease from baseline	0 (0%)	2 (0.1%)	1 (<0.1%)
Phosphate <0.32 mmol/L (<1 mg/dl)	0 (0%)	0 (0%)	0 (0%)
Lab Test, High Extreme Criteria			
Creatinine >265.2 mmol/L (. 3.0 mg/dl)	0 (0%)	0 (0%)	0 (0%)
BUN >14.3 mmol/l (42.7 mg/dl)	0 (0%)	6 (0.2%)	1 (<0.1%)
Chloride >130 mmol/L	0 (0%)	0 (0%)	0 (0%)
Calcium >3.74 mmol/l (>15 mg/dl)	0 (0%)	0 (0%)	0 (0%)
Phosphate >2.42 mmol/L (>7.5 mg/dl)	0 (0%)	0 (0%)	0 (0%)
Urinary Indices			
Urine Protein >1+	16 (1.6%)	44 (1.4%)	9 (0.9%)
Urine Glucose >1+	17 (1.7%)	88 (2.7%)	15 (1.5%)
Urine pH >8.5	0 (0%)	1 (<0.1%)	2 (0.2%)
Urine Ketones >1+	2 (0.2%)	5 (0.1%)	3 (0.3%)
Urine RBCs >10 per HPF	39 (3.9%)	142 (4.4%)	46 (4.5%)
Urine WBCs >20 per HPF	42 (4.2%)	130 (4.0%)	54 (5.3%)

a. Data from NDA Integrated Safety Summary, table 24.1. The database used is the is trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

b. The number of available subjects varied slightly from test to test, within the range of 1080.

c. The number of available subjects varied slightly from test to test, within the range of 3250.

d. The number of available subjects varied slightly from test to test, within the range of 1060.

Table 5.1.4.1.2 Incidence of extreme renal lab values in the open-label, long-term Arthritis trials (OA and RA) from NDA 20-998[a].

	Celecoxib 100-400 mg[b]
Lab Test, Low Extreme Criteria	
Sodium <120 mmol/L	0/4197 (0%)
Potassium <2 meq/L	0/4186 (0%)
Chloride <75 mmol/L	0/4199 (0%)
Calcium <1.7 or 15% decrease from baseline	N/A
Phosphate <0.32 mmol/L	0/4190 (0%)
Lab Test, High Extreme Criteria	
Creatinine >265.2 mmol/L (. 3.0 mg/dl)	1/4376 (<0.1%)
BUN >14.3 mmol/l (42.7 mg/dl)	12/4372 (0.3%)
Chloride >130 mmol/L	0/4199 (0%)
Calcium >3.74 mmol/l	N/A
Phosphate >2.42 mmol/L	0/4190 (0%)
Urinary Indices	
Urine pH >8.5	6/4085 (0.1%)
Urine Protein >1+	91/ 4049 (2.2%)
Urine Glucose >1+	127/ 4023 (3.2%)
Urine Ketones >1+	5/4082 (0.1%)
Urine RBCs >10 per HPF	330/ 3979 (8.3%)
Urine WBCs >20 per HPF	282/ 3971 (7.1%)

a. Data from NDA Integrated Safety Summary, table 24.7, shown for all subjects with OA and RA. The database used is from study 024. The number shown reflects the incidence of any extreme value at any time during the trial The incidence of extreme values at last visit were, in general, lower.

b. The number of available subjects with data varied broadly, and are shown for each lab individually.

Comparison of mean laboratory values

The sponsor also analyzed the labs according to changes in mean values. The table below will focus on the celecoxib 400 mg dose, and will show only the final measurements. Where appropriate, references to other celecoxib doses and time of measurement will be added. Each mean represent data from 400 to 450 subjects. Labs that are not shown found no significant differences between any of the three groups (i.e., calcium, urinary indices).

Table 5.1.4.1.3 Changes in final measured mean labs in the controlled North American Arthritis trials of celecoxib from NDA 20-998[a].

Changes in Final Visit Lab Values from Baseline	Placebo	Celecoxib 400 mg	Active Controls	P-value Celecoxib vs. Placebo	P-value Celecoxib vs. Active Control	P-value Active Control vs. Placebo
Creatinine (μmol/l)	-1.3±0.54	-1.8±0.54	-0.8±0.56	NS	NS	NS
BUN (mmol/l)	-0.57±0.061	0.27±0.063	0.55±0.071	<0.001	0.003	<0.001
Potassium (mmol/l)	-0.03±0.02	0.05±00.02	-0.01±0.02	<0.001	0.013	NS
Chloride (mmol/l)	-0.2±0.17	0.3±0.18	0.0±0.18	0.046	NS	NS
Phosphate (mmol/l)	0.008±0.009	0.010±0.009	-0.042±0.008	NS	<0.001	<0.001

a. Data from NDA Integrated Safety Summary, table 25.1.2. The database used is from studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087. Number of subjects in each measurement varies between 410 and 440 (see table 25.1.2 for details).

These same labs were also examined for the long-term, open-label trial.

Table 5.1.4.1.4 Changes in final measured mean labs in the open-label, long-term Arthritis trials (OA and RA) from NDA 20-998[a].

Changes in Final Visit Lab Values from Baseline	Celecoxib
Creatinine (μmol/l)	0.5±0.18
BUN (mmol/l)	0.28±0.023
Potassium (mmol/l)	0.04±0.006
Chloride (mmol/l)	-0.3±0.05
Phosphate (mmol/l)	0.005±0.0029

a. Data from NDA Integrated Safety Summary, table 25.4. The database used is from trial 024, and includes between 2300 and 2400 subjects (see table 25.4r details).

Shifts of laboratory values among the five categories defined by the extreme and mid-range high and low values for each laboratory test

Finally, the sponsor analyzed the change in lab values within the five defined lab ranges (extremely low, low, normal, high, and extremely high). The table below shows the incidence of maximal shifts from baseline for selected renal labs in the 400 mg BID group. Similar patterns were seen in the 100-200 mg celecoxib group (see NDA Integrated Safety Summary, Appendix 5.1.2 for details).

Table 5.1.4.1.5 Shift in serum lab values in the 12-week, controlled North American Arthritis trials of celecoxib for 400 mg from NDA 20-998[a].

Maximal Change in Lab Value	Placebo	Celecoxib 400 mg	Active Controls
Creatinine (μmol/l)			
High (176.8-265.2 mmol/l)	None	None	None
Extreme high	None	None	None
BUN (mmol/l)			
High (9.3-14.3 mmol/l)	**5/420 from Normal**	**17/409 from Normal**	**21/423 from Normal**
	3/11 from High	**8/10 from High**	**6/11 from High**
Extreme high	None	None	0/1 from Extreme High
Sodium (mmol/l)			
Low (120-135 mmol/l)	11/29 from Low	9/27 from Low	7/21 from Low
	12/398 from Normal	26/385 from Normal	27/401 from Normal
High (140-160 mmol/l)	17/ 398 from Normal	12/385 from Normal	23/401 from Normal
	1/3 from High	1/6 from High	3/12 from High
Extreme High or Low	None	None	None
Potassium (mmol/l)			
Low (2-3.5 mmol/l)	3/6 from Low	4/6 from Low	2/4 from Low
	12/406 from Normal	8/399 from Normal	20/419 from Normal
	1/8 from High	0/12 from High	0/9 from High
High (5-6 mmol/l)	**8/416 from Normal**	**20/399 from Normal**	**20/419 from Normal**
	2/8 from High	**5/12 from High**	**3/9 from High**
Extreme High (>6 mmol/l)	None	None	None
Chloride			
Low (75-90 mmol/l)	0/0 from Low	0/0 from Low	0/0 from Low
	0/413 from Normal	2/408 from Normal	5/407 from Normal
High (110-130 mmol/l)	**19/413 from Normal**	**40/406 from Normal**	**45/407 from Normal**
	4/17 from High	**3/13 from High**	**12/27 from High**
Extreme High or Low	None	None	None
Phosphate			
Low (0.32-0.97 mmol/l)	31/63 from Low	42/70 from Low	62/75 from Low
(1.0 to 3.0 mg/dl)	55/366 from Normal	61/348 from Normal	117/358 from Normal
High (1.61-2.42 mmol/l)	3/366 from Normal	2/348 from Normal	2/358 from Normal
(5.0 to 7.5 mg/dl)	2/2 from High	0/0 from High	0/0 from High
Extreme High or Low	None	None	None

a. Data from NDA Integrated Safety Summary, table 5.1.2. The database used is the is trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.